

**7.02 IRINOTECAN (nanoliposomal),
Solution for I.V. infusion containing nanoliposomal
irinotecan (as sucrosofate) 43 mg in 10 mL,
Onivyde[®],
SERVIER LABORATORIES (AUST.) PTY. LTD.**

1 Purpose of submission

- 1.1 The Standard Re-entry resubmission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing for nanoliposomal irinotecan (nal-IRI), for use in combination with oxaliplatin, 5-fluorouracil (5-FU) and folinic acid/Leucovorin (LV), for the first-line treatment of metastatic pancreatic adenocarcinoma (mPAC). The four-drug chemotherapy regimen is known as NALIRIFOX.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of NALIRIFOX versus a weighted comparator of gemcitabine plus nanoparticle albumin-bound paclitaxel (Gem+NabP) and FOLFIRINOX (non-liposomal irinotecan used in combination with oxaliplatin, 5-FU and LV). The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Previously untreated patients diagnosed with metastatic pancreatic adenocarcinoma
Intervention	NALIRIFOX regimen administered intravenously on days 1 and 15 of each 28-day cycle: <ul style="list-style-type: none"> • nal-IRI 50 mg/m² over 90 minutes • oxaliplatin 60 mg/m² over 120 minutes • LV 50 mg/m²;^a and • 5-FU 2,400 mg/m² over 46 hours
Comparator	Gemcitabine and nanoparticle albumin-bound paclitaxel (Gem + NabP) regimen administered intravenously on days 1, 8 and 15 of each 28-day cycle: <ul style="list-style-type: none"> • Gem 1,000 mg/m² and • NabP 125 mg/m² FOLFIRINOX regimen administered intravenously on days 1 and 15 of each 28-day cycle: <ul style="list-style-type: none"> • irinotecan 180 mg/m² over 90 minutes • oxaliplatin 85 mg/m² over 120 minutes • LV 50 mg and • 5-FU 400 mg/m² followed by 2,400m/m² over 46 hours Mixed comparator approach used in economic evaluation was Gem+NabP (75%) and FOLFIRINOX (25%)
Outcomes	Primary endpoint: overall survival (OS) Secondary endpoints: progression-free survival (PFS); objective response rate (ORR); Health-related quality of life (HRQoL) Safety
Clinical claim	<u>Gem + NabP:</u> NALIRIFOX is superior in terms of effectiveness compared to Gem+NabP NALIRIFOX has a different safety profile compared to Gem+NabP, however it should not be concluded that one safety profile is superior or inferior to the other <u>FOLFIRINOX:</u> NALIRIFOX is superior in terms of effectiveness (PFS and OS) compared to FOLFIRINOX NALIRIFOX appears to have advantages in terms of incidence of haematological adverse events, including the sequelae of those effects (e.g., infection), compared to FOLFIRINOX.

Source: Compiled during the evaluation using Table 1.7, p12 of the resubmission, Table 2.2, p19 of the resubmission and Section 2 of the resubmission.

Abbreviations: 5-FU, 5-fluorouracil; FOLFIRINOX, fluorouracil, folinic acid, irinotecan, oxaliplatin; Gem, gemcitabine; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HRQoL, health-related quality of life; LV, Leucovorin (folinic acid); nal-IRI, nanoliposomal irinotecan; NabP, nanoparticle albumin-bound paclitaxel; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

^a LV dose in NALIRIFOX has been changed from 400 mg/m² to a flat dose of 50 mg from previous submission to reflect recommendations as per eviQ consensus statement. This dose differed from the dose used in the NAPOLI-3 trial (400 mg/m²).

Blue shading indicates information previously seen by the PBAC.

2 Background

Registration status

2.1 Nal-IRI is TGA registered as follows:

- in combination with oxaliplatin and 5-fluorouracil (5-FU) and leucovorin (LV) for the first-line treatment of metastatic pancreatic adenocarcinoma.
- in combination with 5-FU and LV for the treatment of metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.

Previous PBAC consideration

2.2 Nal-IRI was previously considered for the proposed indication in March 2024. The PBAC did not recommend listing on the basis that FOLFIRINOX was the relevant main comparator in the proposed population, rather than Gem+NabP as nominated by the submission. The PBAC considered that the submission had not established superiority of NALIRIFOX to FOLFIRINOX. The PBAC considered there is a high clinical need for new effective treatments for pancreatic cancer, however the submission’s clinical claims were not supported by the clinical evidence (para 7.1, irinotecan (nanoliposomal), Public Summary Document [PSD], March 2024 PBAC meeting). The main PBAC concerns and how they were addressed in the resubmission are summarised in the table below.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addressed it
Restriction	The PBAC noted that the proposed restriction, which permitted the use of NALIRIFOX in patients with an ECOG PS score ≤ 2, was aligned with the PBS restriction for NabP. However, the PBAC considered that access should be limited to patients with ECOG PS 0 to 1, consistent with the clinical evidence supporting its use (the NAPOLI-3 trial), and consistent with clinical practice guidelines such as the NCCN guidelines (para 7.4, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).	Addressed. The proposed PBS restriction was amended to ECOG PS 0 to 1 to align with the NAPOLI-3 trial and clinical practice guidelines.
	The PBAC had previously determined that second-line use of nal-IRI was associated with an unacceptably high incremental cost for modest and uncertain incremental clinical benefit (para 2.4, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). The submission asked the PBAC to consider allowing sequential use by removing the criterion that limits use of these treatments (nal-IRI and NabP) to the first line setting.	Not addressed. The resubmission proposed to limit the use of nal-IRI to patients who have not been treated previously with PBS-subsidised therapy (i.e. first-line setting). The issue remains that if NALIRIFOX is recommended for first line (and as Gem+NabP is listed for first line only) – then it means a patient may only receive only one option or the other. The Pre-Sub-Committee Response (PSCR, pg. 1) reiterated the original submission proposed that patients should be able to switch regimens if clinically appropriate.
Comparator	The PBAC considered that the submission’s nomination of Gem+NabP as main comparator was inappropriate, because the population in which NALIRIFOX will be used is closer to the population treated with FOLFIRINOX (para 7.6, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). The PBAC noted that characteristics of this population may include younger age and good performance status (ECOG PS 0 to 1). The PBAC considered that FOLFIRINOX was the appropriate main comparator for NALIRIFOX for the proposed	Not addressed. The resubmission presented a mixed comparator of Gem+NabP (75%): FOLFIRINOX (25%). This was based on estimates of the market share of these regimens as first line treatments for patients with mPAC and an ECOG-PS 0-1 in Australia using data from the PURPLE registry (85.1% Gem+NabP and 14.9% FOLFIRINOX) and assumptions that NALIRIFOX would substitute for up to █████% of patients treated with Gem+NabP and up to █████% of patients treated with

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Component	Matter of concern	How the resubmission addressed it
	<p>listing (para 7.6, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p> <p>While the submission proposed that NALIRIFOX would become the preferred first line treatment option for patients that are currently treated with Gem+NabP for mPAC, the PBAC considered that many of the Gem+NabP patients would not be suitable for treatment with NALIRIFOX, due to its toxicity profile, which is more similar to that of FOLFIRINOX than Gem+NabP (para 7.5, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p>	<p>FOLFIRINOX. This approach is inconsistent with the previous view expressed by the PBAC at its March 2024 meeting. The ESC considered FOLFIRINOX to be the appropriate main comparator consistent with the prior advice of the PBAC.</p>
<p>Comparative effectiveness of NALIRIFOX vs Gem+NabP</p>	<p>The PBAC considered the clinical claim of superior effectiveness of NALIRIFOX over Gem+NabP was supported by the data, although the magnitude was small and may not be clinically meaningful (para 7.8, irinotecan, PBAC PSD, March 2024 PBAC meeting).</p>	<p>Not adequately addressed.</p> <p>The resubmission provided additional OS outcome data from the NAPOLI-3 trial with a longer follow up period (29 months vs 16 months from previous submission). However, the results were very similar to those presented in the March 2024 submission (Hazard ratio [HR]= 0.84 [95% CI 0.72, 0.98], compared to HR=0.83 [95% CI 0.70-0.99] in the March 2024 submission; the reported median increase in OS of 1.9 months in the NALIRIFOX arm did not change between submissions).</p> <p>Challenging the PBAC's previous consideration that the improvement in OS of NALIRIFOX vs Gem+NabP may not be clinically meaningful, the resubmission argued that the ASCO minimal clinically important difference (MCID) referenced in the March 2024 PBAC PSD (a range of 3 to 5 months as the MCID in OS and PFS over standard therapy) are aspirational rather than intended to serve as rigid thresholds to apply in decision-making.¹</p>
<p>Comparative safety of NALIRIFOX vs Gem+NabP</p>	<p>The PBAC considered that the claim of non-inferior comparative safety of NALIRIFOX versus Gem+NabP was not adequately supported by the data, due to increased rates of drug related serious adverse events, as well as all-cause and drug-related TEAEs leading to interruption of treatment, for NALIRIFOX patients in NAPOLI-3 compared with Gem+NabP (para 7.9, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p>	<p>Not adequately addressed.</p> <p>The resubmission acknowledged that the safety profiles of the two regimens are different and that there is a higher risk of gastrointestinal disorders, asthenia, and hypokalaemia but also a lower risk of haematologic toxicity in the NALIRIFOX arm compared to the Gem+NabP arm. The resubmission stated that gastrointestinal toxicity can impact quality of life, hydration and nutritional status, and haematologic toxicity often represent treatment-limiting adverse events and can lead to infections, fatigue and bleeding issues. The</p>

¹ Ellis et al., (2014). 'American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes', J Clin Oncol, 32(12), 1277-80.
<https://ascopubs.org/doi/10.1200/JCO.2013.53.8009>

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	<p>The PBAC also noted that the safety profiles of NALIRIFOX and Gem+NabP were different. The PBAC considered that higher rates of gastrointestinal toxicities such as diarrhoea and nausea with NALIRIFOX would be significant for patients and impact quality of life (para 7.9, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p>	<p>resubmission contended that, overall, it cannot be concluded that one safety profile is superior or inferior to the other.</p> <p>No additional safety data was presented in the resubmission to support the safety claim however further discussion was provided. Previous concerns and limitations to safety data remain.</p>
<p>Comparative effectiveness and safety of NALIRIFOX and FOLFIRINOX</p>	<p>The PBAC considered the submission had not established the superiority of NALIRIFOX to FOLFIRINOX (para 7.1, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p> <p>The PBAC noted that both the PSCR and Pre-PBAC response presented a single-step ITC for OS using data from the recently presented GENERATE trial, which directly compared FOLFIRINOX with Gem+NabP. The PBAC noted the ESC's concerns around the GENERATE trial (such as differences between treatment arms in patient and disease characteristics, the use of a modified FOLFIRINOX regimen that may bias against FOLFIRINOX, and inadequate reporting of analysis methodology). The PBAC noted further concerns including the higher proportion of patients discontinuing due to AEs with FOLFIRINOX (34.3% versus 23.9% for Gem+NabP) and longer median OS for Gem+NabP in GENERATE trial versus other trials. The PBAC noted the ITC based on the GENERATE trial had not been evaluated, however due to multiple concerns, considered that it was unreliable (para 7.12, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p>	<p>Effectiveness: Not addressed</p> <p>The resubmission conducted a single-step indirect treatment comparison (ITC) using the Bucher method and a matching-adjusted indirect comparison (MAIC) of NALIRIFOX and FOLFIRINOX for OS, PFS and AEs using the results from the GENERATE trial (same data presented in March 2024 submission) and updated OS results from the NAPOLI-3 trial.</p> <p>The resubmission stated that the results of the single-step ITC and the MAIC suggest that NALIRIFOX is superior in terms of impact on both PFS and OS compared to the modified FOLFIRINOX regimen administered in the GENERATE trial.</p> <p>Safety: Not addressed</p> <p>Indirect comparison of the incidence of AEs for NALIRIFOX vs FOLFIRINOX were conducted. The resubmission indicated that the indirect comparisons in relation to haematological AEs consistently favoured NALIRIFOX and the difference was statistically significant for neutropenia and for infections.</p> <p>The evidence from the GENERATE trial has not changed since the March 2024 submission. This remains based on an abstract and a presentation in the European Society for Medical Oncology (ESMO) congress on 22 October 2023 that have limited supporting information available.</p> <p>There are many differences between the GENERATE and NAPOLI-3 trials that were not accounted for in the MAIC and single-step ITCs presented in this resubmission, which posed transitivity issues and may lead to confounding. Overall, when accounting for these issues and uncertainties, the assumption of transitivity was likely violated for the comparison of NALIRIFOX and FOLFIRINOX using the data from the GENERATE study; therefore, the ITCs should not be considered robust.</p> <p>Previous concerns of the GENERATE trial</p>

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		<p>regarding the comparability due to differences in patient and disease characteristics, the higher proportion of patients discontinuing due to AEs with FOLFIRINOX, the substantially longer median OS reported with Gem+NabP compared to other trials, and inadequate reporting of details of the trial remain unresolved.</p>
Economic model	<p>The PBAC did not consider the cost utility analysis comparing NALIRIFOX and Gem+NabP to be informative because it considered that FOLFIRINOX was the appropriate main comparator. The PBAC noted the submission also presented alternative modelled scenarios to incorporate FOLFIRINOX as a comparator in a proportion of patients, which assumed that NALIRIFOX was superior to FOLFIRINOX. The PBAC considered these scenarios were not informative as they relied on the clinical claim of superior efficacy of NALIRIFOX over FOLFIRINOX, a claim which it considered was not supported (para 7.13, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting)</p> <p>The PBAC considered that a resubmission would need to nominate FOLFIRINOX as the main comparator, and if there was insufficient evidence to support a claim of superiority of NALIRIFOX over FOLFIRINOX in terms of efficacy or safety, the appropriate form of economic evaluation would be a cost-minimisation approach (para 7.15, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting)</p>	<p>Not adequately addressed</p> <p>The resubmission incorporated FOLFIRINOX as part of a mixed comparator (75% Gem+NabP and 25% FOLFIRINOX) in a cost-utility analysis.</p> <p>The clinical claim that NALIRIFOX is superior in terms of effectiveness compared to FOLFIRINOX was not adequately supported by the indirect evidence presented. The comparative effectiveness of NALIRIFOX vs FOLFIRINOX was a key driver of the ICER in the economic evaluation.</p> <p>There was also considerable uncertainty in the estimates of the proportions of the mixed comparator, which was a key driver of the ICER in the economic evaluation.</p>
Financial estimates	<p>The PBAC considered that the submission's assumption that NALIRIFOX would replace Gem+NabP in up to 85% of patients was not reasonable, and that replacement of FOLFIRINOX should have been modelled. The PBAC noted that the estimates were highly sensitive to the medicines replaced, and the additional cost was not justified as the submission had not demonstrated clinical superiority over the most relevant comparator, which was FOLFIRINOX (para 7.14, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).</p>	<p>Not adequately addressed.</p> <p>The resubmission assumed uptake of NALIRIFOX will result from the substitution of up to [REDACTED] % of the Gem+NabP market (which represents 85.1% of the total market) and up to [REDACTED] % of the NALIRIFOX market (which represents the remaining 14.9% of the total market).</p> <p>The estimated market share of Gem+NabP and FOLFIRINOX (as analysed by the PURPLE registry) may be overestimated based on a similar analysis in a report by Lee 2023 which identified that approximately 22% of patients with locally advanced, recurrent or metastatic pancreatic adenocarcinoma had first-line chemotherapy treatment other than Gem+NabP and FOLFIRINOX. Additionally, there is uncertainty in the extent to which Gem+NabP and FOLFIRINOX</p>

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		<p>may be substituted by NALIRIFOX in clinical practice; the proposed substitution rate of 50% of Gem+NabP is likely too high based on the toxicity profile of NALIRIFOX and the lack of a clinically meaningful difference in effectiveness.</p> <p>Collectively, this has resulted in the uptake rate of NALIRIFOX and subsequent financial estimates likely being overestimated.</p>

Source: Compiled during the evaluation

Abbreviations: AEs, adverse events; ASCO, American Society of Clinical Oncology; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESMO, European Society for Medical Oncology; FOLFIRINOX, fluorouracil, folinic acid, irinotecan, oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NabP, nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; MCID, minimal clinically important difference; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; NCCN, National Comprehensive Cancer Network; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PFS, progression-free survival; PSD, public summary document; PURPLE; Pancreatic cancer: Understanding Routine Practice & Lifting End registry; TEAEs, treatment emergent adverse events.

2.3 Nal-IRI has also been considered by the PBAC for use in the second-line setting:

- November 2016: Submission requested use in combination with 5-FU and folinic acid for the treatment of mPAC in adult patients with disease progression who have previously received gemcitabine-based therapy. The PBAC did not recommend listing on the basis of unacceptably high incremental cost for a modest and uncertain incremental clinical benefit (para 7.1, irinotecan (nanoliposomal), PSD, November 2016 PBAC meeting).
- March 2018: Resubmission requested use in combination with 5-FU and folinic acid for the treatment of patients with mPAC who have previously failed gemcitabine-based therapy. The PBAC did not recommend listing on the basis of unacceptably high incremental cost for a modest and uncertain incremental clinical benefit (para 6.1, irinotecan (nanoliposomal), PSD, March 2018 PBAC meeting).

3 Requested listing

3.1 The requested listing is shown below. Changes compared to the March 2024 submission are shown in italics.

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	No. of Rpts
Nanoliposomal Irinotecan 43mg/10mL injection, 10mL vial	Published price: Public: \$3,990.13 Private: \$4,089.40 Effective price: Public: \$ ██████ Private: \$ ██████	110 mg	9
Available brands			

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ONIVYDE®, Servier Laboratories (Aust.) Pty. Ltd Nanoliposomal Irinotecan 43mg/10mL injection, 10mL vial
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Source: Table 1.8, p15 of the resubmission.

Abbreviations: Amt, amount; Aust., Australia; Max, maximum; №, Number; Rpts, repeats.

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists
Restriction type: Authority Required (STREAMLINED)
Administrative Advice: Not for use as neoadjuvant or adjuvant therapy.
Administrative Advice: Special Pricing Arrangements apply
Severity: Stage IV (metastatic)
Condition: Adenocarcinoma of the pancreas
Indication: Stage IV (metastatic) adenocarcinoma of the pancreas
Clinical criteria: The treatment must be in combination with oxaliplatin, 5-fluorouracil and folinic acid (Leucovorin)
AND
Clinical criteria: The condition must not have been treated previously with PBS-subsidised therapy,
AND
Clinical criteria: <i>Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less.</i>
Prescribing instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
Caution: <i>Nanoliposomal irinotecan is not equivalent to non-liposomal irinotecan formulations and should not be interchanged.</i>

Source: Table 1.9, p16 of the resubmission.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PBS, Pharmaceutical Benefits Scheme.

Changes compared to the original submission in *italics*

- 3.2 The proposed maximum amount for nal-IRI is 110 mg, based on the recommended dose of 50 mg/m² and a maximum body surface area of 2.2 m². The proposed number of repeats (nine) would provide patients with a total of five cycles of treatment, which is consistent with the median number of cycles of nal-IRI (five) in the NAPOLI-3 trial. The proposed maximum amount and repeats have not changed from March 2024 submission.
- 3.3 The resubmission proposed an effective DPMA of \$████ (public) and \$████ (private) for nal-IRI for the proposed maximum amount (110 mg). These effective DPMA are █% lower (public) and █% lower (private) than the effective DPMA from the March 2024 submission.
- 3.4 The current DPMA for non-liposomal irinotecan on the PBS is \$160.13 (public) and \$205.80 (private) for a maximum amount of 800 mg.
- 3.5 The resubmission has amended the proposed restriction to limit eligibility to patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 1 or less, consistent with PBAC advice. This aligns with the clinical evidence supporting its use (the NAPOLI-3 trial) and is consistent with clinical practice guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines.
- 3.6 This resubmission proposed to limit the use of nal-IRI to patients who have not been treated previously with PBS-subsidised therapy (i.e. first-line setting). The issue

remains that if NALIRIFOX is recommended for first line use (and as Gem+NabP is listed for first line only), then a patient may only receive only one option or the other. The Pre-Sub-Committee Response (PSCR) stated the Sponsor was aware of this issue and reiterated the original submission proposed that patients should be able to switch regimens if clinically appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Pancreatic adenocarcinoma (PAC) is a cancer of the exocrine pancreas. Pancreatic cancer is a disease with high morbidity and mortality and is the eighth most commonly diagnosed cancer in Australia.²
- 4.2 Pancreatic cancer is difficult to detect in its early stages, and patients may remain asymptomatic until the advanced stages of the disease. Approximately 20% of patients diagnosed with PAC present with disease that is limited to the pancreas and potentially resectable (Stage I-II), while approximately 50% present with metastatic disease (Stage IV; mPAC).^{3,4} The remaining 30% present with disease that interfaces with major vascular structures, making it either borderline resectable or locally advanced/unresectable (stage III).^{5,6} Due to the typically late diagnosis, pancreatic cancer is overrepresented in mortality and is estimated to be the fourth leading cause of cancer-related death in Australia. The three-year survival for patients with mPAC at diagnosis is 4%, and overall PAC three-year survival is 11%.⁷
- 4.3 The treatment approach for PAC is dependent on the stage of the cancer and the treatment goals of the patient and their family.⁸ Surgical resection remains the only possibility of cure. However, most patients (80% or more) are not suitable for surgery at the time of diagnosis.⁹ The treatment of mPAC is with chemotherapy or best supportive care (BSC). Chemotherapy in this context is not administered with curative

² Australian Institute of Health and Welfare, (2023), 'Cancer data in Australia, Cancer rankings data visualisation', <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/rankings>

³ Tempero MA, Malafa MP et al, (2017), 'Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology', J Natl Compr Can Netw, 2017;15(8):1028–61

⁴ Bockhorn M, Uzunoglu FG et al, (2014), 'Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS)', Surgery, 2014;155(6):977–88

⁵ Malik NK, May KS et al, (2012), 'Treatment of locally advanced unresectable pancreatic cancer: a 10-year experience', J Gastrointest Oncol, Dec;3(4):326-34

⁶ Puckett Y, Garfield K, (2023), 'Pancreatic Cancer', Available from: <https://www.ncbi.nlm.nih.gov/books/NBK518996/>

⁷ Cabasag C.J., Arnold M et al, (2022), 'Pancreatic cancer survival by stage and age in seven high-income countries (ICBP SURVMARK-2): a population-based study', Br J Cancer 126, 1774–1782 (2022)

⁸ Loveday BPT, Lipton L et al, (2019), 'Pancreatic cancer: An update on diagnosis and management', Aust J Gen Pract. 2019 Dec;48(12):826-831

⁹ Kleeff J, Korc M et al, (2016), 'Pancreatic cancer', Nat. Rev. Dis. Primers 2, 16022.

intent. It is administered with the aims of controlling the rate of growth of the cancer, relieving symptoms, maintaining or improving quality of life, and prolonging survival.

- 4.4 There are multiple chemotherapy regimens that are used for the first-line treatment of mPAC. Australian registry data suggest that the most frequently used regimens for first line mPAC are Gem+NabP (66.5% of patients), FOLFIRINOX (10.9%) and gemcitabine monotherapy (10.3%).¹⁰
- 4.5 Nal-IRI injection is a liposomal formulation that encapsulates irinotecan, a topoisomerase I inhibitor, inside a lipid bilayer vesicle. The encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to its active metabolite, SN-38. The nanoliposomal formulation of irinotecan demonstrates higher intra-tumoural concentrations,^{11,12} thus in theory minimising systemic toxicity as compared with standard formulation irinotecan. The TGA Delegate’s Overview (p22) stated “there was no direct clinical evidence demonstrating that liposomal encapsulation changes the clinical efficacy or safety of irinotecan for the general population of patients with pancreatic cancer”.
- 4.6 Nal-IRI (as part of NALIRIFOX regimen) is proposed as a first-line chemotherapy for the treatment of mPAC in patients with good performance status (ECOG PS of 0-1). This differed from the March 2024 submission, which included mPAC patients with good and intermediate performance status (ECOG PS 0-2).

For more detail on PBAC’s view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission proposed a mixed comparator of Gem+NabP (75%) and FOLFIRINOX (25%). The main argument provided by the resubmission in support of this nomination was that Gem+NabP is substantially more commonly used than FOLFIRINOX in patients with mPAC (Stage III or IV) and ECOG PS of 0 or 1 (85.1% vs 14.9%, respectively), based on Australian data from the Pancreatic cancer: Understanding Routine Practice & Lifting End (PURPLE) registry. The nominated comparator differed from the March 2024 submission, which included Gem+NabP as the main comparator (100%) and FOLFIRINOX as a secondary (minor) comparator.
- 5.2 At the March 2024 meeting, the PBAC noted that Gem+NabP is currently the most frequently used treatment in the first-line setting, however the PBAC considered that the submission’s nomination of Gem+NabP as main comparator was inappropriate because the population in which NALIRIFOX will be used is closer to the population

¹⁰ Lee, B, (2023), ‘Use of Metastatic Pancreatic Cancer Treatment Algorithms in Routine Clinical Practice in Australia - a PURPLE Translational Registry study’

¹¹ Barbier et al., (2020), ‘Differentiation of liposomal irinotecan from dose-dense non-liposomal irinotecan in patient-derived pancreatic cancer xenograft tumor models’, J Clin Oncol, 38:e16724

¹² Kalra et al., (2014), ‘Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor pro-drug conversion’, Cancer Res, 74(23):7003-13

treated with FOLFIRINOX (para 7.6, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). The PBAC noted that characteristics of this population may include younger age and good performance status (ECOG PS 0 to 1). The PBAC considered that FOLFIRINOX was the appropriate main comparator for NALIRIFOX for the proposed listing (para 7.6, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).

- 5.3 The resubmission claimed there was no evidence to support the PBAC’s advice that clinicians will preferentially use NALIRIFOX in younger or fitter patients compared with Gem+NabP (para 7.6, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). The resubmission however did accept the advice of the PBAC with regard to limiting the eligible population to those with an ECOG PS of 0 or 1, which differs from the population in whom Gem+NabP can be used, as the restriction for NabP includes patients with an ECOG PS of 2 (gemcitabine has an unrestricted PBS listing).
- 5.4 The resubmission argued the NAPOLI-3 trial results supported the use of NALIRIFOX in a broader patient population (older) than the population currently treated with FOLFIRINOX (younger and fitter) and maintained that NALIRIFOX will be used in a proportion of patients who would currently use Gem+NabP. Furthermore, the resubmission argued that while NALIRIFOX and FOLFIRINOX regimens have similar components, there are differences in the dose intensity of the individual drugs (higher doses of irinotecan, oxaliplatin and 5-FU in FOLFIRINOX) that translate to differences in the safety profile associated with each regimen. The resubmission maintained that haematological toxicity is the key reason FOLFIRINOX is usually reserved for use in patients with a very good ECOG PS (typically younger) patients. The resubmission stated that the FOLFIRINOX protocol listed in the NSW eviQ cancer treatment guidelines indicated that FOLFIRINOX “is potentially a toxic regimen and should be used in patients with normal albumin, bilirubin and a very good ECOG performance status. Strategies to minimise toxicity include granulocyte colony-stimulating factor (G-CSF) support, dose attenuation (e.g., omitting 5FU bolus and/or reducing irinotecan to 150 mg/m²), thorough patient education and vigilant monitoring for any potential septic episodes”.¹³
- 5.5 The proposed weighted comparator approach was inconsistent with the previous view expressed by the PBAC at its March 2024 meeting. At that time, the PBAC advised that a resubmission would need to nominate FOLFIRINOX as the main comparator, and if there was insufficient evidence to support a claim of superiority of NALIRIFOX over FOLFIRINOX in terms of efficacy or safety, the appropriate form of economic evaluation would be a cost minimisation approach (paragraph 7.15, irinotecan (nanoliposomal) PSD, March 2024 PBAC meeting).

¹³ EviQ, (2022), ‘Pancreas metastatic FOLFIRINOX (modified) (fluorouracil leucovorin irinotecan oxaliplatin)’, <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary/1512-pancreas-metastatic-folfirinox-modified-fl>

- 5.6 The PSCR argued that a cost-minimisation approach versus FOLFIRINOX, as suggested by the PBAC, is inappropriate given the resubmission's claim that NALIRIFOX will displace the use of Gem+NabP in clinical practice. The PSCR also discussed that a cost-minimisation approach would result in a lower price for NALIRIFOX than Gem+NabP which it considered inappropriate when there is RCT evidence showing superior OS for NALIRIFOX over Gem+NabP. The ESC did not agree with the PSCR's arguments and considered that the main comparator and therapy most likely to be replaced in practice would be FOLFIRINOX (rather than Gem+NabP).
- 5.7 The resubmission did not provide sufficient evidence to address the PBAC's previous considerations regarding the comparative effectiveness and safety of NALIRIFOX over FOLFIRINOX (discussed further in the Section 6). As such, the evaluation considered the use of the mixed comparator approach was not supported based on the available evidence.
- 5.8 The PSCR argued the PURPLE registry data indicated that Gem+NabP remained the most often used option for patients with a good performance status (ECOG 0-1). Combined with the claim of superior comparative effectiveness to Gem+NabP, the PSCR maintained that NALIRIFOX will mostly substitute for that treatment regimen in practice.
- 5.9 The ESC agreed with the evaluation and considered, consistent with the prior advice of the PBAC, that FOLFIRINOX was the appropriate main comparator. The ESC considered that as a claim of superior comparative effectiveness and/or safety of NALIRIFOX over FOLFIRINOX was not supported (discussed further in Section 6), that the weighted comparator approach taken by the submission was inappropriate. Furthermore, given a claim of superiority was not supported, the ESC considered that the appropriate form of economic evaluation to determine the price of nal-IRI would be a cost minimisation approach versus FOLFIRINOX.
- 5.10 The ESC considered, given its view on the clinical claim versus FOLFIRINOX not being adequately supported, that Gem+NabP would only be considered the comparator if a cohort of patients who are clinically unsuitable for FOLFIRINOX but suitable for NALIRIFOX could be defined and quantified within the requested population. The ESC noted no such subpopulation had been identified by the submission. The ESC noted that utilisation data presented from the PURPLE registry did not identify patients who were clinically unsuitable for FOLFIRINOX, and therefore did not provide any basis for the resubmission's assumption that if nal-IRI was available, the population treated with Gem+NabP would reduce by half.
- 5.11 The resubmission derived the weighting of the mixed comparator (75%/25%) based on an assumption that $\frac{1}{2}$ % of patients with ECOG PS 0-1 currently treated with Gem+NabP (85.1% of the market share) and $\frac{1}{2}$ % of patients currently treated with FOLFIRINOX (14.9% of the market share) would be suitable for treatment with NALIRIFOX.

- 5.12 Issues with the weighted comparator approach notwithstanding, the proposed comparator weighting between Gem+NabP and FOLFIRINOX is also uncertain. A report by Lee 2023 which included an analysis of PURPLE registry data investigating treatment patterns for patients with locally advanced, recurrent or metastatic pancreatic adenocarcinoma who received first line chemotherapy identified the following proportions of treatment regimens: Gem+NabP (67%), FOLFIRINOX (11%) and other first line therapies (22%). As such, the market share of Gem+NabP and FOLFIRINOX presented in the resubmission (85.1% and 14.9% respectively) may be overestimated. The PSCR stated that a retrospective study at one hospital in Western Australia (Talbot et al. 2023, indicated a higher proportion of Gem+NabP use (92/95=96.8%) than FOLFIRINOX (3/95=3.2%) in practice, and argued that the market share of Gem+NabP assumed in the resubmission may be underestimated.
- 5.13 The ESC agreed with the evaluation that market share data of treatments for mPAC from other countries where NALIRIFOX has been launched could be helpful to support the resubmission's assumptions that NALIRIFOX will substitute for up to █% of patients treated with Gem+NabP and █% of patients treated with FOLFIRINOX. The PSCR stated that no such data were available.
- 5.14 The PSCR reiterated that the PURPLE registry indicates that the therapy most often used for patients with an ECOG PS of 0 or 1 is Gem+NabP. It also stated that the median age and age range of patients recruited to the NAPOLI-3 trial (65 years, with a range of 20-85) matches those treated with Gem+NabP in Australian clinical practice rather than those for the cohort of patients treated with FOLFIRINOX. The median age (range) of patients treated with Gem+NabP and FOLFIRINOX in the PURPLE registry was 67 (33-88) and 59 (30-87) years, respectively. The ESC noted that while the age characteristics of the NAPOLI-3 population appeared closer to the PURPLE registry Gem+NabP population, based on data presented in the PSCR, this did not mean that the populations were the same across other characteristics. The ESC considered that clinical trial patients and registry patients are not comparable, in the sense that individuals choosing to participate in clinical trials are typically a relatively fit subset of the overall population. The ESC considered that the choice of treatment is not as simple as age and ECOG PS when a patient with cancer has a poor prognosis, the toxicity of the drugs is significant and must be weighed against the expected benefit for the individual. The Pre-PBAC Response argued more effective options are needed to help address the unmet need in mPAC and reiterated that NALIRIFOX is an option that has been demonstrated to be superior to Gem+NabP and also reiterated the submission arguments that Gem+NabP was the therapy most likely to be replaced in practice.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The Sponsor requested a hearing for this item. The clinician discussed the populations who are likely to be considered for NALIRIFOX and Gem+NabP and stated there was a substantial overlap (except for ECOG 2 status) in who could be considered for either therapy. The clinician also discussed the results of the NAPOLI-3 trial and stated the gains in terms of survival were significant and that other measures beyond median overall survival, such as landmark survival, hazard ratio and progression free survival were also important and the results of these were more strongly in favour of NALIRIFOX. In addition, the clinician discussed the adverse event profiles of NALIRIFOX and Gem+NabP, stating that with increased experience in using nal-IRI, managing the gastrointestinal side effects had become easier and that it had fewer neuropathy and haematological side effects than Gem+NabP.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (11) and organisations (5) via the Consumer Comments facility on the PBS website. The comments from individuals discussed the effectiveness of irinotecan on tumour size, outlined the side effects while on treatment, and the improvements in physical activity and reduced pain after treatment. The comments from health care professionals highlighted the burden of suffering due to mPAC, especially in younger patients, and described NALIRIFOX as being able to be used in the first or second line settings, with an acceptable toxicity profile and further noted that Australian registry studies corroborate the survival benefits associated with second-line treatments.
- 6.3 The PBAC welcomed the input from consumer organisations the Australian Pancreatic Cancer Foundation (PanKind), the Pancare Foundation and Rare Cancers Australia, all supporting the listing of nal-IRI. The Committee noted the input from PanKind discussed the devastating impact of pancreatic cancer and low 5-year survival rates, and shared testimonials from patients and family members about the hopelessness and desperation for better and more affordable treatments. The PBAC noted the input from the Pancare Foundation similarly highlighted the poor prognosis in pancreatic cancer and outlined that pancreatic cancer is often diagnosed late, and patients experience a range of serious side effects as a consequence of the cancer and its available treatment options, with those side effects and the focus on treatment leading to people having to cease working and rely more on carers as the condition progresses. The Committee also noted the input from Rare Cancers Australia, that described how many view a pancreatic cancer diagnosis as being handed a 'death sentence' due to the poor prognosis, and outlined that NALIRIFOX is the first treatment in over a decade to demonstrate a significant survival benefit for patients with previously untreated mPAC in a Phase III trial.
- 6.4 The PBAC acknowledged the input from medical organisation WA Medical Oncology,

that was a centre for the NAPOLI-3 trial and stated the benefits of NALIRIFOX over Gem+NabP in terms of both overall survival and progression free survival were statistically and clinically significant in the first line mPAC setting.

- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its support for the nal-IRI resubmission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nal-IRI, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹⁴.

Clinical trials

- 6.6 The resubmission was based on one randomised controlled trial (RCT) comparing NALIRIFOX with Gem+NabP: NAPOLI-3 trial (N=770), and one RCT comparing mFOLFIRINOX with Gem+NabP: JCOG1611-GENERATE (herein referred to as GENERATE; N=476) trial. No head-to-head trials were available for comparison between NALIRIFOX and FOLFIRINOX, therefore indirect treatment comparisons (ITCs) using Gem+NabP as the common comparator were presented. These trials have already been reviewed by the PBAC at the March 2024 meeting, however the available information for the GENERATE trial is limited to an abstract, a deck of presentation slides and a published protocol (Misusawa 2022)¹⁵.
- 6.7 Compared to the March 2024 submission, the main differences in the clinical evidence presented in the resubmission were:
- Inclusion of updated results for the overall survival (OS) outcome from the NAPOLI-3 trial (patient-level data and poster presented at the 2024 American Society of Clinical Oncology (ASCO) annual meeting) based on the data cut on 3 October 2023 with a longer median follow up of 29.5 months (compared to 16.1 months in the March 2024 submission). Despite the longer follow-up period, the difference in median OS remains unchanged (para 6.22).
 - Inclusion of a single-step ITC and a matching-adjusted indirect comparison (MAIC) for NALIRIFOX vs FOLFIRINOX for OS, progression-free survival (PFS) and adverse events (AEs) based on the NAPOLI-3 (using updated OS data) and GENERATE (using the same data presented in March 2024 submission) trials. The previous submission presented a ‘side by side’ (unanchored) ITC and a multistep ITC was conducted during the evaluation, based on the NAPOLI-3, MPACT and

¹⁴ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

¹⁵ Mizusawa, J., Ohba, A., et al. (2023). Protocol of a randomized phase II/III study of gemcitabine plus nab-paclitaxel combination therapy versus modified FOLFIRINOX versus S-IROX for metastatic or recurrent pancreatic cancer: JCOG1611 (GENERATE). *Japanese Journal of Clinical Oncology*. 53(1), 80-84. <https://doi.org/10.1093/jjco/hyac146>

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ACCORD11/PRODIGE4 trials. A single-step ITC for OS based on NAPOLI-3 and GENERATE trial was presented in the PSCR and Pre-PBAC response.

6.8 The resubmission stated that the selection of the trials for the ITC was based on specification from the PBAC guidelines that indicated that shorter links are preferred in the conduct of ITCs. The evaluation considered this reason is inadequate to justify the exclusion of the broader evidence base. Data from the MPACT and ACCORD11/PRODIGE4 trials were not used in the ITCs presented in the resubmission, however, data from these trials may be relevant given the lack of direct comparative evidence and the deficiencies of the available information for the GENERATE trial (see para 6.10).

6.9 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
NAPOLI-3 NCT04083235	An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas. Wainberg et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. Hussein et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): updated overall survival analysis with 29-month follow-up of NAPOLI -3	CSR March 2023 Lancet 2023; 402(10409):1272-1281. American Society of Clinical Oncology (ASCO) Annual Meeting 2024.
JCOG1611- GENERATE jRCTs031190009	Mizusawa et al. Protocol of a randomized phase II/III study of gemcitabine plus nab-paclitaxel combination therapy versus modified FOLFIRINOX versus S-IROX for metastatic or recurrent pancreatic cancer: JCOG1611 (GENERATE) Obha et al. Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): a multicenter, randomized, open-label, three-arm, phase 2/3 trial	Japanese Journal of Clinical Oncology 2023; 53(1):80-84 European Society for Medical Oncology (ESMO) Congress October 2023. Abstract 16160
MPACT NCT00844649	Von Hoff et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.	N Engl J Med. 2013; 369(18):1691-703
ACCORD11/PRODIGE4 NCT00112658	Conroy et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.	N Engl J Med. 2011; 364(19):1817-25

Source: Table 2.1, p18 of the resubmission.

Abbreviations: ASCO, American Society of Clinical Oncology; CSR, clinical study report; ESMO, European Society for Medical Oncology; FOLFIRINOX, 5-fluorouracil, leucovorin/folinic acid, standard irinotecan, and oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; nab, nanoparticle albumin-bound; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; N Eng J Med, The New England Journal of Medicine; S-IROX, S-1, irinotecan, and oxaliplatin

Blue shading indicates information previously seen by the PBAC.

6.10 The evidence from the GENERATE trial has not changed since the March 2024 submission. This remains based on an abstract and a presentation in the European

Society for Medical Oncology (ESMO) congress on 22 October 2023 that lack sufficient details. In March 2024, the PBAC noted the ESC's concerns around the GENERATE trial (such as differences between treatment arms in patient and disease characteristics, the use of a modified FOLFIRINOX regimen that may bias against FOLFIRINOX, and inadequate reporting of analysis methodology). The PBAC noted further concerns including the higher proportion of patients discontinuing due to adverse events (AEs) with FOLFIRINOX (34.3% versus 23.9% for Gem+NabP) and longer median OS for Gem+NabP in GENERATE trial versus that observed in other trials. The PBAC previously noted the ITC based on the GENERATE trial had not been evaluated, however due to multiple concerns, considered that it was unreliable (para 7.12, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).

- 6.11 In March 2024, the ESC and PBAC noted a recent publication comparing NALIRIFOX, FOLFIRINOX and Gem+NabP as first-line chemotherapy for mPAC (Nichetti et al. 2024; para 6.11, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).¹⁶ This analysis included data from relevant arms of the NAPOLI-3, ACCORD11/PRODIGE4 and MPACT trials, as well as the following trials that were not included in the March 2024 submission and resubmission: HALO (Gem+NabP), RESOLVE (Gem+NabP), AVENGER500 (FOLFIRINOX) and CanStem111P (Gem+NabP). The analysis of OS and progression-free survival (PFS) was based on pooled individual patient data (IPD) extracted from Kaplan-Meier (KM) plots of original trials via a graphic reconstructive algorithm, while the analysis of objective response rate (ORR) and Grade ≥ 3 AEs was based on pooled data from each treatment arm/trial. The resubmission contended that the analyses reported by Nichetti et al. 2024 are not an appropriate basis for determining the comparative efficacy and safety of NALIRIFOX and FOLFIRINOX, citing methodological limitations in that no attempt was made to adjust for differences in patient-level covariates across the different trials included in the analysis, which may affect the pooled results. The resubmission did not agree with the publication's assertion that "the risk of bias due to these limitations should be minimal" was justified and argued that there are more appropriate indirect comparisons available, particularly those using GENERATE presented in the resubmission.
- 6.12 The key features of the trials are summarised in Table 4.

¹⁶ Nichetti F et al. (2024) 'NALIRIFOX, FOLFIRINOX, and Gemcitabine With Nab-Paclitaxel as First-Line Chemotherapy for Metastatic Pancreatic Cancer: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7(1):e2350756. doi: [10.1001/jamanetworkopen.2023.50756](https://doi.org/10.1001/jamanetworkopen.2023.50756)

Table 4: Key features of the included evidence

Trial	N	Design Median duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
NALIRIFOX vs Gem+NabP						
NAPOLI-3	770	R, OL, MC, MN, phase 3 NALIRIFOX & Gem+NabP 29.5 months for OS 16.1 month for PFS, ORR, HRQoL, Safety	Some concerns	mPAC not previously treated with chemotherapy	OS, PFS, ORR, HRQoL, Safety	OS, PFS, HRQoL
Gem+NabP vs FOLFIRINOX (vs S-IROX)						
GENERATE	527	R, OL, MC (Japan), phase 2/3 Gem+NabP: NR FOLFIRINOX: NR	At least some concerns ^a	Metastatic or recurrent PAC not previously treated with chemotherapy	OS, PFS, ORR, Safety	OS, PFS
Gem+NabP vs Gemcitabine						
MPACT	861	R, OL, MC, MN, phase 3 Gem+NabP: 9.1 months Gem: 7.4 months	Some concerns	mPAC not previously treated with chemotherapy	OS, PFS, ORR, Safety	NA
FOLFIRINOX vs Gemcitabine						
PRODIGE4	342	R, OL, MC (France), phase 2/3 FOLFIRINOX & Gem 26.6 months	Some concerns	mPAC not previously treated with chemotherapy	OS, PFS, ORR, Safety	NA

Source: Table 2.2, p19 of the resubmission.

Abbreviations: FOLFIRINOX, 5-fluorouracil, folinic acid, irinotecan and oxaliplatin; Gem+NabP = gemcitabine, nab-paclitaxel; HRQoL, health-related quality of life; MC, multicentre; MN, multinational; mPAC, metastatic pancreatic adenocarcinoma; NA, not applicable; NALIRIFOX, 5-fluorouracil, folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NR, not reported; OL, open-label; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomised; S-IROX, S-1, irinotecan, and oxaliplatin.

^a The overall risk of bias for the GENERATE trial is of at least some concerns because there were some concerns about the risk of attrition bias, however, the risk of reporting bias remains unclear as the outcome evidence presented in this resubmission was based on an abstract and presentation slides that lack sufficient details.

Blue shading indicates information previously seen by the PBAC.

- 6.13 The NAPOLI-3, MPACT, and ACCORD11/PRODIGE4 were considered to have an overall risk of some concerns due to risk of detection bias and attrition bias (para 6.9, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). This remains unchanged.
- 6.14 Discontinuation was high in the GENERATE trial (85.7% FOLFIRINOX and 81.2% Gem+NabP with a higher proportion of patients discontinuing due to AEs with FOLFIRINOX [34.3% vs 23.9% for Gem+NabP]) before early trial termination (Ohba et al. 2023). This would lead to some concerns in reporting bias. Further, the characteristics of these patients were not provided, and this raises some concerns about the risk of attrition bias.
- 6.15 The following differences in the inclusion criteria, baseline characteristics, study design and setting between the NAPOLI-3 and GENERATE trials were identified, which raises concerns regarding the exchangeability of the trials and robustness of the indirect comparisons performed in the resubmission.
- The GENERATE trial was a single country study with all study sites located in Japan, while the NAPOLI-3 trial was a multinational study with study sites across North America, South America, Europe, Asia, Israel and Australia.

- Patients in the GENERATE trial tended to be older (56.4% over 65 years) than those in the NAPOLI-3 trial (50% over 65 years).
- A small proportion of patients of Asian heritage (4.9%) were included in the NAPOLI-3 trial while all patients (100%) of the GENERATE trial were of Asian heritage. Asian heritage has been associated with longer overall survival for PAC compared to non-Asian heritage and this may be due to genetic and molecular differences (e.g., different KRAS genes and p53 gene expression).^{17 18}
- Patients in the GENERATE trial had a better performance status (ECOG PS 0) than patients in the NAPOLI-3 trial (67.2% vs 44%).
- The proportion of patients who had liver metastases was higher in the NAPOLI-3 trial (80.3%) compared with GENERATE trial (68.7%).
- The proportion of patients who had ≥ 2 metastatic sites at baseline was higher in the NAPOLI-3 trial compared to the GENERATE trial (67.3% vs 37.6%). The number of metastatic sites has been found to be an independent prognostic factor for OS in patients with mPAC.¹⁹
- A higher proportion of patients with cancer antigen 19-9 (CA 19-9) levels ≥ 37 units/mL in the NAPOLI-3 than in the GENERATE trial (83% vs 79.5%). Elevated levels of CA19-9 have been associated with reduced survival for PAC.^{20 21 22}

6.16 The resubmission noted that characteristics including age over 65 years, high performance status and the presence of liver metastases were found to be independent prognostic factors of poor outcomes in mPAC. The combined impact of the identified differences and prognostic factors on observed outcomes are uncertain. The PSCR highlighted results from a subgroup analysis of OS from the NAPOLI-3 trial presented in the resubmission which showed that the OS hazard ratio (HR) favoured NALIRIFOX over Gem+NabP in all subgroups, including those aged ≥ 65 years (vs < 65 years) and those with ECOG PS of 1 (vs 0) (Figure 1 of the PSCR).

¹⁷ Olakowski M. & Bułdak Ł. (2022), 'Modifiable and Non-Modifiable Risk Factors for the Development of Non-Hereditary Pancreatic Cancer', *Medicina (Kaunas)*, 58(8):978. doi: 10.3390/medicina58080978.

¹⁸ Anama-Green C. & Quinn M. (2021), 'Survival Analysis of Demographic Factors Associated With 5+ Year Survival of Pancreatic Carcinoma', *Cureus*, 13(1):e13032. doi: 10.7759/cureus.13032.

¹⁹ Wu et al. (2021), 'Clinical significance of site-specific metastases in pancreatic cancer: a study based on both clinical trial and real-world data', *Journal of Cancer*, 12(6), 1715-1721. <https://doi.org/10.7150/jca.50317>.

²⁰ Le N. & Sund M. (2016), 'Prognostic and predictive markers in pancreatic adenocarcinoma', *Digestive and Liver Disease*, 48 (3), 223-230. <https://doi.org/10.1016/j.dld.2015.11.001>

²¹ Li et al. (2022), 'Prognosis and survival analysis of patients with pancreatic cancer: retrospective experience of a single institution'. *World J Surg Oncology*, 20, 11 (2022). <https://doi.org/10.1186/s12957-021-02478-x>

²² Hartwig et al. (2013), 'CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy', *Ann Surg Oncol*. 2013 Jul;20(7):2188-96. doi: 10.1245/s10434-012-2809-1.

6.17 A key difference between the NALIRIFOX and FOLFIRINOX regimens across the trials were the doses used. Table 5 summarises the dosages of drugs used in FOLFIRINOX and NALIRIFOX regimens in the clinical trials, as well as recommended dosing of FOLFIRINOX in Australia and the proposed dosing for NALIRIFOX presented in the resubmission.

Table 5: Summary of NALIRIFOX and FOLFIRINOX regimens proposed in the resubmission and used in the different trials and in Australia.

Component	FOLFIRINOX (ACCORD11/PRODIGE4 trial) ^a	mFOLFIRINOX (GENERATE trial) ^b	mFOLFIRINOX (Recommended in Australia)	NALIRIFOX (NAPOLI-3 trial) ^a	NALIRIFOX (Proposed) ^b
Oxaliplatin	85 mg/m ²	85 mg/m ²	85 mg/m ²	60 mg/m ²	60 mg/m ²
Irinotecan	180 mg/m ²	150 mg/m ²	180 mg/m ²	50 mg/m ² (liposomal)	50 mg/m ² (liposomal)
Leucovorin/folinic acid	400 mg/m ²	200 mg/m ²	50 mg	400 mg/m ²	50mg
5-fluorouracil (bolus)	400 mg/m ²	None	400 mg/m ²	None	None
5-fluorouracil	2400 mg/m ²	2400 mg/m ²	2400 mg/m ²	2400 mg/m ²	2400 mg/m ²

Source: Produced during the evaluation using Table 1.7, p12 of resubmission, Conroy et al 2011, Ohba et al 2023, Wainberg et al 2023 and Australian eviQ guidelines.²³

Abbreviations: FOLFIRINOX, 5-fluorouracil, Leucovorin/folinic acid; irinotecan and oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX; mg/m², milligrams per metre squared; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin.

^a Used in the March 2024 submission

^b Used in the November 2024 resubmission

6.18 The resubmission proposed a new LV dose of 50 mg as part of NALIRIFOX regimen based on advice that when NALIRIFOX is added to the Australian eviQ guidelines, a flat 50 mg dose of LV will be recommended to be consistent with the following eviQ consensus statement: "Given the lack of evidence on the optimum dose of LV when administered with 5-FU, and evidence suggesting similar therapeutic efficacy, a flat dose of 50 mg LV has been included in relevant eviQ colorectal and upper gastrointestinal protocols based on reference committee consensus".²⁴ This is different from the PI and NAPOLI-3 trial, which included a dose of LV of 400 mg/m² over 30 minutes. Given this, it is likely the low LV dose of 50 mg will be the standard protocol for NALIRIFOX and will apply to all patients.

6.19 The modified FOLFIRINOX (mFOLFIRINOX) regimen in the GENERATE trial differs from the FOLFIRINOX regimen in the ACCORD11/PRODIGE4 trial and from the

²³ eviQ (2022), 'Pancreas metastatic FOLFIRINOX (modified) (fluorouracil leucovorin irinotecan oxaliplatin)', <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary/1512-pancreas-metastatic-folifirinox-modified-fl>

²⁴ EviQ, (2022), 'Folinic acid (calcium folinate or Leucovorin®): low dose or high dose', <https://www.eviq.org.au/additional-clinical-information/3065-folinic-acid-calcium-folinate-or-leucovorin>

mFOLFIRINOX regimen recommended in the Australian eviQ guidelines²⁵(Table 5). The mFOLFIRINOX regimen in the GENERATE trial has lower doses of irinotecan and 5-FU (reduction of 16.6% and 14.8%, respectively) compared to ACCORD11/PRODIGE4 trial and eviQ guidelines. The evaluation considered that a 15-20% dose reduction of irinotecan (or any other component) is unlikely to significantly affect the efficacy and toxicity of the FOLFIRINOX regimen. Evidence suggests that dosage attenuation of initial FOLFIRINOX improves its tolerability without compromising its efficacy and that mFOLFIRINOX could provide comparative survival benefits with fewer adverse events compared to the conventional dosage.²⁶

Comparative effectiveness

NALIRIFOX versus Gem+NabP

6.20 A summary of the updated efficacy results for OS, PFS and ORR from the intention to treat (ITT) population in NAPOLI-3 trial is presented in Table 6, with the corresponding KM curves of OS and PFS presented in Figure 1 and Figure 2. Results for PFS and ORR remain unchanged from March 2024 submission.

Table 6: Results of OS, PFS and ORR in the ITT population in NAPOLI-3 trial

	NALIRIFOX N=383	Gem+NabP N=387
New evidence presented in this resubmission		
Median follow-up, months	29.5	
OS		
Death, n (%)	328 (85.6)	345 (89.1)
Censored, n (%)	55 (14.4)	42 (10.9)
Event free probability, n, % (95% CI)		
3 months	NR	NR
6 months	72.4 (67.6, 76.6)	68.4 (63.5, 72.8)
9 months	58.1 (53.0, 62.9)	51.8 (46.7, 56.7)
12 months	45.6 (40.5, 50.5)	39.6 (34.7, 44.5)
18 months	26.6 (22.2, 31.1)	20.0 (16.1, 24.1)
Median (95% CI), months	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI; p-value)	0.84 (0.72, 0.98; p=0.026)	
Unstratified HR (95% CI; p-value)	0.85 (0.73, 0.98; p=0.029)	
Evidence in the March 2024 submission		
Median (95% CI) follow-up, months	16.0 (15.0, 16.8)	16.3 (15.0, 17.5)
OS		
Death, n (%)	259 (67.6)	285 (73.6)
Censored, n (%)	124 (32.4)	102 (26.4)
Event free probability, n, % (95% CI)		
3 months	319, 84.2 (80.2, 87.5)	315, 82.5 (78.3, 86.0)

²⁵ eviQ (2022), 'Pancreas metastatic FOLFIRINOX (modified) (fluorouracil leucovorin irinotecan oxaliplatin)', <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary/1512-pancreas-metastatic-folfirinox-modified-fl>

²⁶ Tong et al. (2018), 'The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis', *Sci Rep* 8, 8666. <https://doi.org/10.1038/s41598-018-26811-9>

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	NALIRIFOX N=383	Gem+NabP N=387
6 months	274, 72.4 (67.6, 76.6)	261, 68.4 (63.5, 72.8)
9 months	220, 58.1 (53.0, 62.9)	196, 51.8 (46.7, 56.7)
12 months	162, 45.6 (40.5, 50.5)	140, 39.5 (34.6, 44.4)
18 months	32, 26.2 (20.9, 31.7)	28, 19.3 (14.8, 24.2)
Median (95% CI), months	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI; p-value)	0.83 (0.70, 0.99; p=0.04)	
Unstratified HR (95% CI; p-value)	0.84 (0.71, 0.99; p=0.04)	
PFS		
Median (95% CI) follow-up, months	16.0 (15.0, 16.8)	16.3 (15.0, 17.5)
Patients with PFS Event, n (%)	249 (65.0)	259 (66.9)
PD	183 (47.8)	176 (45.5)
Death	66 (17.2)	83 (21.4)
Censored, n (%)	134 (35.0)	128 (33.1)
Event free probability, n, % (95% CI)		
3 months	248, 76.9 (72.1, 81.1)	240, 71.5 (66.5, 75.9)
6 months	164, 56.4 (50.7, 61.6)	112, 43.2 (37.6, 48.6)
9 months	113, 40.9 (35.3, 46.4)	55, 24.9 (19.8, 30.2)
12 months	61, 27.4 (22.3, 32.7)	19, 13.9 (9.7, 18.9)
18 months	9, 11.4 (7.1, 16.9)	1, 3.6 (0.5, 12.3)
Median (95% CI), months	7.4 (6.0, 7.7)	5.6 (5.3, 5.8)
Stratified HR (95% CI; p-value)	0.69 (0.58, 0.83; p<0.0001)	
Unstratified HR (95% CI; p-value)	0.69 (0.58, 0.83; p<0.0001)	
ORR		
BOR, n (%)		
CR	1 (0.3)	1 (0.3)
PR	159 (41.5)	139 (35.9)
SD	99 (25.8)	101 (26.1)
PD	38 (9.9)	56 (14.5)
NE	86 (22.5)	90 (23.3)
ORR (CR or PR), n (%)	160 (41.8)	140 (36.2)
95% CI	(36.8, 46.9)	(31.4, 41.2)
OR (95% CI; p-value)	1.26 (0.95, 1.69; p = 0.11)	

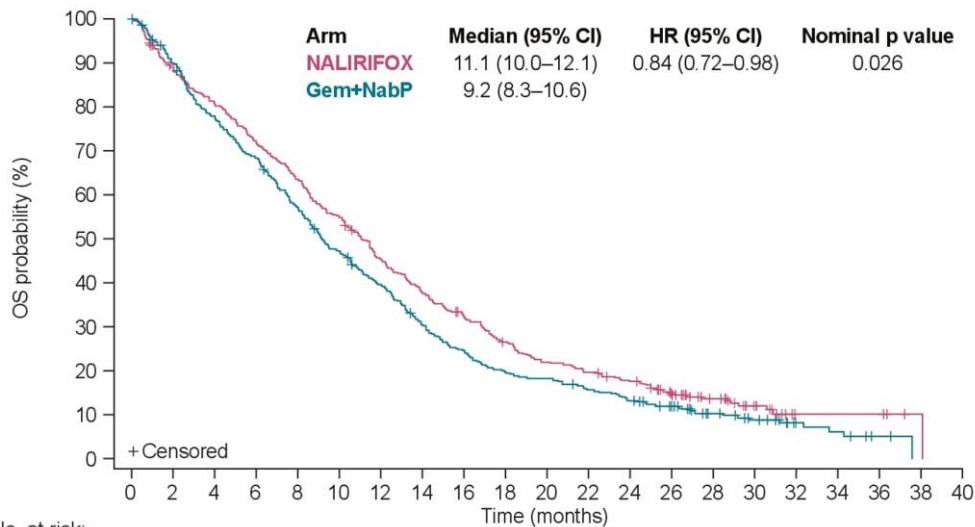
Source: Table 2.4, Table 2.6, pp21-23 of resubmission and Table 32, p69 of March 2024 submission.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention to treat; NabP, nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NE, not evaluable; NR, not reported; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, Progression free survival; PR, partial response; SD, stable disease.

Note: Results in **bold** indicate statistically significant difference (p < 0.05).

Blue shading indicates information previously seen by the PBAC.

Figure 1: Kaplan-Meier Curves of Overall Survival (ITT) in NAPOLI-3 trial (median follow up: 29.5 months)



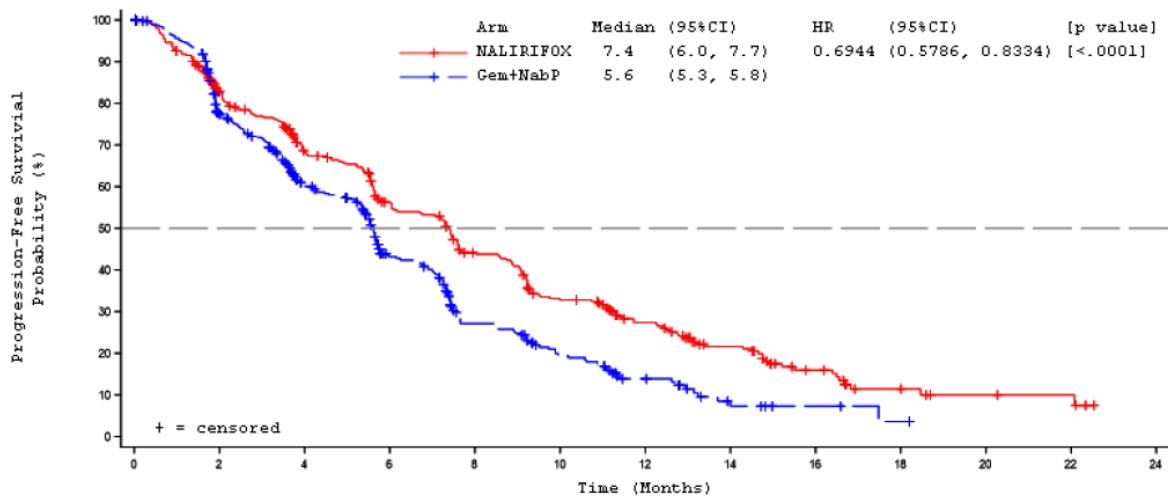
No. at risk:

NALIRIFOX	383	337	308	274	241	209	171	142	121	97	80	72	62	45	29	17	5	5	5	1	0
Gem+NabP	387	345	298	261	218	179	148	113	91	74	67	57	48	38	24	17	8	6	2	0	0

Source: Figure 2.3, p23 of resubmission.

Abbreviations: CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; ITT, intention to treat; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OS, overall survival.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival (ITT) in NAPOLI-3 trial (median follow-up: 16.1 months)



No. at Risk:

NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
Gem+NabP	387	267	182	112	60	38	19	6	3	1	0	0	0

Source: Figure 2.2, p22 of resubmission.

Abbreviations: CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; ITT, intention to treat; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin.

Blue shading indicates data previously seen by the PBAC.

6.21 NALIRIFOX showed a statistically significant improvement in OS compared with Gem+NabP (Hazard ratio [HR] 0.84; 95% confidence interval [CI]: 0.72, 0.98; p-value = 0.026). The median OS was 11.1 months (95% CI: 10.0, 12.1) for the NALIRIFOX arm and 9.2 months (95% CI: 8.3, 10.6) for the Gem+NabP arm, with a difference of 1.9 months in median OS. The difference of 1.9 months between NALIRIFOX and Gem+NabP is similar to the OS results presented in the March 2024 submission

- (1.9 months gain [HR 0.83; 95% CI: 0.70, 0.99; p-value = 0.04]), which the PBAC considered to be small and may not be clinically meaningful (para 7.8, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).
- 6.22 The resubmission contended that an almost 2-month improvement in PFS and OS is highly probable, meaningful and of high value to patients and their families. The resubmission argued that the ASCO minimal clinically important difference (MCID) referenced in the March 2024 PBAC PSD (a range of 3 to 5 months as the MCID in OS and PFS over standard therapy for mPAC) are aspirational rather than intended to serve as rigid thresholds to apply in decision-making given the following statement from ASCO: “The conclusions reached by the working groups are not intended to set standards for regulatory approval or insurance coverage but rather to encourage patients and investigators to demand more from clinical trials”.²⁷ The resubmission argued that survival improvements of NALIRIFOX over Gem+NabP observed in the NAPOLI-3 trial, was considered meaningful by Australian medical oncologists ((Cooray and Zalcborg 2024)²⁸.
- 6.23 The clinical relevance of the improvements observed in the NAPOLI-3 trial was raised in a commentary published in the Lancet Journal,²⁹ which indicated that the ESMO identified a minimum 3-month benefit in overall survival, and by the World Health Organization (WHO), which recommended a 4–6-month threshold for benefit in overall survival without detriment to quality of life.^{30 31} These thresholds were not met in NAPOLI-3 trial. The magnitude of improvement in PFS and OS presented in the resubmission continues to be small and previous concerns raised in the March 2024 PBAC meeting about the clinical meaningfulness of these improvements remain.
- 6.24 The PSCR argued that in a condition like mPAC where patient prognosis is poor, that the observed benefit of almost 2 months improvement in PFS and OS will be meaningful to patients, and argued the ASCO MCID referenced previously by the PBAC was 'aspirational'. The PSCR further noted the resubmission included a statement from two oncologists (see paragraph 1.1) stating the improvement in OS, as-observed

²⁷ Ellis et al., (2014). 'American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes', J Clin Oncol, 32(12), 1277-80. <https://ascopubs.org/doi/10.1200/JCO.2013.53.8009>

²⁸ Cooray, P., Zalcborg, J. (2024). First-line treatments for metastatic pancreatic cancer: Overview of key trials shaping the treatment landscape in Australia. Key Opinions in Medicine. Available online at <https://keyopinions.info/downloads/first-line-treatments-for-metastatic-pancreatic-cancer/>

²⁹ Besselink MG. & Wilmink JW. (2023), 'Treating metastatic pancreatic ductal adenocarcinoma: NALIRIFOX as new standard?', The Lancet; Published online 11 September 2023. DOI: [https://doi.org/10.1016/S0140-6736\(23\)01521-0](https://doi.org/10.1016/S0140-6736(23)01521-0)

³⁰ Cherny et al. (2015), 'A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)', Ann Oncol. 2015 Aug;26(8):1547-73. doi: 10.1093/annonc/mdv249.

³¹ Jenei et al. (2022), 'Cancer medicines on the WHO Model List of Essential Medicines: processes, challenges, and a way forward', Lancet Glob Health. 2022 Dec;10(12):e1860-e1866. doi: 10.1016/S2214-109X(22)00376-X.

in NAPOLI-3, was a clinically meaningful result. The ESC considered the question of whether such an improvement in PFS and OS would be clinically meaningful to patients, when balanced with the adverse event profiles of NALIRIFOX and Gem+NabP and quality of life considerations, was complex and multifaceted. However, the ESC reiterated issues with comparator selection and comparative effectiveness and safety to FOLFIRINOX were the more substantive issues with the resubmission. The Pre-PBAC Response stated that based on the extended follow-up data from NAPOLI-3, for every 100 patients treated with NALIRIFOX over Gem+NabP, an additional 5 patients would be alive at 36 months, and argued that in conjunction with an improvement in quality of life, is meaningful for people living with mPAC.

- 6.25 Patient-reported outcomes were presented using the EuroQol 5-dimension health status questionnaire 5 level (EQ-5D-5L) Visual Analogue Scale (VAS) for health and EQ-5D-5L index scores for each treatment arms and unchanged from the previous submission. At most time points, the EQ-5D-5L VAS and EQ-5D-5L index scores appear to numerically favour NALIRIFOX over Gem+NabP, although the difference was not statistically significant .

NALIRIFOX versus FOLFIRINOX

- 6.26 The resubmission presented a single-step ITC of the efficacy (OS and PFS) using the Bucher method and a MAIC of NALIRIFOX and FOLFIRINOX using RCT evidence from NAPOLI-3 (updated data) and GENERATE trials.
- 6.27 The methodology for the MAIC was based on the National Institute for Health and Care Excellence (NICE) guidance³² which involved using logistic propensity score model to reweight individual patient-level data (IPD) for OS from the NAPOLI-3 trial to mimic the population recruited to the GENERATE trial for which only aggregate results are available. Using these weights, HRs comparing PFS and OS for NALIRIFOX vs Gem+NabP were predicted for the population in the GENERATE trial and were used in the MAIC against results from the NAPOLI-3 trial. The covariates included in the model were patient age group (< 65 and ≥ 65), ECOG PS (0 or 1) and absence/presence of liver metastases.
- 6.28 Table 7 summarises the results of the single-step ITC and MAIC using the reweighted population.

³² Phillippo et al. (2018), 'Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal', *Med Decis Making*. 2018 Feb;38(2):200-211. doi: 10.1177/0272989X17725740

Table 7: Indirect comparisons of PFS and OS using updated data from the NAPOLI-3 and GENERATE trials

ITCs	NAPOLI-3		GENERATE	
	NALIRIFOX N= 383	Gem+NabP N = 387	mFOLFIRINOX N = 171	Gem+NabP N = 174
Median PFS, in months (95% CI)	7.4 (6.0, 7.7)	5.6 (5.3, 5.8)	5.8 (5.1, 6.9)	6.7 (5.7, 7.4)
Median OS, in months (95% CI)	11.1 (10.0, 12.1) ^a 11.1 (10.0, 12.1) ^b	9.2 (8.3, 10.6) ^a 9.2 (8.3, 10.6) ^b	14.0 (11.4, 16.3)	17.0 (14.5, 18.9)
NALIRIFOX vs mFOLFIRINOX	Single-step ITC		MAIC	
PFS HR (95% CI)	0.60 (0.45, 0.81)		0.53 (0.39, 0.72)	
OS HR (95% CI)	0.65 (0.48, 0.89)		0.66 (0.47, 0.92)	

Source: Table 2.10, p45 of resubmission.

Abbreviations; CI, confidence interval; mFOLFIRINOX, modified 5-fluorouracil, leucovorin/folinic acid, standard irinotecan, and oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect treatment comparison; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OS, overall survival; PFS, progression free survival.

^a Based on median follow-up: 16.1 months

^b Based on median follow-up: 29.5 months

Note: Results in **bold** indicate statistically significant difference.

Blue shading indicates information previously seen by the PBAC

- 6.29 Based on the single-step ITC and MAIC presented by the resubmission, NALIRIFOX showed a statistically significant improvement for NALIRIFOX in OS (HR 0.65; 95% CI: 0.48, 0.89 and HR 0.66; 95% CI: 0.47, 0.92, respectively) and in PFS (HR 0.60; 95% CI: 0.45, 0.81 and HR 0.53; 95% CI: 0.39, 0.72, respectively) compared with mFOLFIRINOX.
- 6.30 Previous concerns of the GENERATE trial raised by the PBAC regarding the comparability due to differences in patient and disease characteristics, the higher proportion of patients discontinuing due to AEs with mFOLFIRINOX, the substantially longer median OS reported with Gem+NabP compared to other trials (e.g. 17.0 months in GENERATE versus 9.2 months in NAPOLI-3), and inadequate reporting of details of the trial remain (para 7.12, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). Another concern was that the improvement in median OS of approximately 3 months for Gem+NabP compared with FOLFIRINOX that was reported for the GENERATE trial, was longer than the improvement in median PFS of approximately one month, which the PBAC previously considered may reflect the OS results being impacted by subsequent treatments (para 7.12, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).
- 6.31 In addition to the issues and uncertainties identified with the GENERATE trial, there are also important differences between NAPOLI-3 and GENERATE that may impact the robustness of these indirect comparisons:
- Different trial settings and eligibility criteria were not accounted for, possibly leading to potential confounding.
 - The MAIC did not adequately account for differences in baseline characteristics and included only three out of six variables in the weights. Asian heritage, CA 19-9 levels, and number of metastatic sites remained unadjusted and this increases the possibility of residual confounding.
 - The resubmission did not report all baseline characteristics and distributions of weights after weighting (including means as well as standard deviations and/or

ranges), which would be useful to assess if study populations of NAPOLI-3 and GENERATE trial are comparable/balanced after weighting.

6.32 Table 8 summarises the OS and PFS results from the multi-step ITC conducted during the evaluation of the March 2024 submission using NAPOLI-3, MPACT and ACCORD11/PRODIGE4 trials along with Nichetti et al. (2024) results presented in the March 2024 PSCR and pre-PBAC response and compares this to the results of the single-step ITC and MAIC presented in the resubmission using the GENERATE trial.

Table 8: Comparison of ITC results: March 2024 submission and current resubmission

	March 2024 PBAC consideration		November 2024 Resubmission	
	NALIRIFOX vs FOLFIRINOX (multistep ITC) ^a	FOLFIRINOX vs NALIRIFOX (Nichetti et al. 2024) ^b	NALIRIFOX vs mFOLFIRINOX (single-step ITC) ^c	NALIRIFOX vs mFOLFIRINOX (MAIC) ^c
	HR>1 favour FOLFIRINOX	HR>1 favour NALIRIFOX	HR<1 favour NALIRIFOX	HR<1 favour NALIRIFOX
PFS HR (95% CI)	1.01 (0.72, 1.43)	1.21 (0.86, 1.70)	0.60 (0.45, 0.81)	0.53 (0.39, 0.72)
OS HR (95% CI)	1.05 (0.76, 1.46)	1.06 (0.81, 1.39)	0.65 (0.48, 0.89)	0.66 (0.47, 0.92)

Source: Compiled during the evaluation using Table 2.13, p49 of resubmission, Nichetti et al 2024 and Table 6, para 6.35 of the March 2024 meeting PSD.

Abbreviations: (m)FOLFIRINOX, (modified) 5-fluorouracil, Leucovorin/folinic acid; irinotecan and oxaliplatin; HR, hazard ratio; ITC, indirect treatment comparison; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OS, overall survival; PFS, progression-free survival.

Statistically significant differences shown in **bold** (p<0.05).

^a Multistep ITC using NAPOLI-3, MPACT and ACCORD11/PRODIGE4 trials.

^b Nichetti et al. (2024) conducted an ITC using NAPOLI-3, MPACT, ACCORD11/PRODIGE4, HALO, RESOLVE, AVENGER500 and CanStem111P trials.

^c Based on NAPOLI-3 and GENERATE trials.

Blue shading indicates information previously seen by the PBAC

6.33 The results of the multistep ITC and Nichetti et al. (2024) presented in the March 2024 PBAC meeting suggested no statistically significant difference for OS (HR 1.05; 95% CI: 0.76, 1.46 and HR 1.06; 95% CI: 0.81-1.39, respectively) and PFS (HR 1.01; 95% CI: 0.72, 1.43 and HR 1.21; 95% CI: 0.86-1.70, respectively) between NALIRIFOX and FOLFIRINOX. This differed from the results of the single-step ITC and MAIC presented in the resubmission (using GENERATE trial results) which suggest a statistically significant improvement for NALIRIFOX in OS and in PFS compared with mFOLFIRINOX.

6.34 While the MAIC methodology is theoretically more robust than the methodologies applied in March 2024 and the single step ITC presented in the resubmission, there are important limitations that may impact the ITC results:

- As described in paragraph 6.32, there are many differences (e.g. study design, patient characteristics) between the GENERATE and NAPOLI-3 trials with some important differences not accounted for in the MAIC and single-step ITCs presented in this resubmission and in the March 2024 PSCR, which represent transitivity issues and may lead to confounding.
- Key issues relating to the use of the GENERATE trial (para 6.10). Given that the ITCs relied upon the GENERATE trial, the robustness of the results of the ITCs is uncertain.

- For the multistep ITC considered by the PBAC in March 2024, there were potential transitivity issues related to the differences in trial design, setting and baseline characteristics such as age, performance status, metastatic disease burden and liver metastases between NAPOLI-3, MPACT and ACCORD11/PRODIGE4 trials. The combined impact of the identified differences on observed outcomes are uncertain.
 - The ITC conducted by Nichetti et al (2024) involved reconstruction of IPD from the included trials and there was no adjustment for differences in patient-level covariates. The authors acknowledged that heterogeneity among the populations of the different trials may affect the pooled results.
- 6.35 The PSCR argued the resubmission’s approach of presenting a one-step ITC and MAIC of NALIRIFOX and FOLFIRINOX using the NAPOLI-3 and GENERATE trials (with Gem+NabP as the common comparator) was valid and that factors such as differences in race between these studies and other variables were prognostic variables rather than treatment effect modifiers; therefore, relative treatment effect measures like hazard ratios would remain stable. Further, the PSCR argued the inherent limitations of ITCs are further compounded when a multi-step ITC (as-presented in Table 8) is conducted, and that there are extensive differences between NAPOLI-3, MPACT and ACCORD11/PRODIGE4 that contribute to high uncertainty in that analysis. The PSCR also argued the methodology of Nichetti 2024 also undermined the validity of the outcomes of that analysis.
- 6.36 The ESC acknowledged there were methodological weaknesses with the ITCs presented, however was of the view that there was insufficient information available to conclude the GENERATE study was either sufficiently exchangeable with NAPOLI-3 (and the existing evidence base) for a reliable ITC to be conducted, or generalisable to the Australian mPAC population. The ESC noted GENERATE remained available only as a conference abstract, and the issues identified above, as well as being carried out in a single country with known differences to the Australian context, the notably longer OS outcome reported for the Gem+NabP arm compared to the existing evidence base and the use of a different FOLFIRINOX regimen to Australian practice all substantially undermined the exchangeability of GENERATE to the other available trial evidence. Therefore, the ESC did not consider the results of the ITC of NALIRIFOX and FOLFIRINOX using the GENERATE trial to be reliable. The ESC also noted that the ITCs presented in the resubmission included less patients than the ITCs considered by the PBAC in March 2024.
- 6.37 The ESC recalled that the March 2024 submission did not present a formal statistical comparison between NALIRIFOX and FOLFIRINOX however an unanchored indirect comparison of OS based on the NALIRIFOX arm of the NAPOLI-3 trial, and the FOLFIRINOX arm of the ACCORD11/PRODIGE4 trial prepared during the evaluation, suggested no difference in efficacy between the treatments (median OS of 11.1 months for both treatments). A multistep ITC (with both gemcitabine and Gem+NabP as common comparators) also suggested no difference between

NALIRIFOX and FOLFIRINOX for OS (HR 1.05; 95% CI 0.76, 1.46), which was a similar result to the analysis by Nichetti et al (2024) described above (HR 1.06; 95% CI 0.81, 1.39). Based on these analyses, the ESC considered that the submission's clinical claim of superior effectiveness of NALIRIFOX over FOLFIRINOX was not supported.

- 6.38 The Pre-PBAC Response noted the results of another RCT of Gem+NabP vs. FOLFIRINOX (PASS-01) had become available, with early results presented at the ASCO Gastrointestinal Cancers Symposium in June 2024, which, like GENERATE, found a modest improvement in outcomes for Gem+NabP over FOLFIRINOX (PFS 5.1 vs 4 mo (p=0.14), OS 9.7 vs 8.4mo (p=0.04). The Response provided data including a conference abstract (Knox 2024)³³ and a link to a recording of the ASCO symposium presentation³⁴ however this lacked sufficient details for further evaluation.

Comparative harms

NALIRIFOX versus Gem+NabP

- 6.39 While overall rates of adverse events were similar across both arms in NAPOLI-3, the PBAC considered in March 2024, that the claim of non-inferior comparative safety of NALIRIFOX versus Gem+NabP was not adequately supported by the data, due to increased rates of drug-related serious adverse events, as well as all-cause and drug-related TEAEs leading to interruption of treatment, for NALIRIFOX patients in NAPOLI-3 compared with Gem+NabP. Safety data presented in the resubmission remain unchanged from the March 2024 submission.
- 6.40 Table 9 presents a summary of the frequency of treatment emergent adverse events (TEAEs). A summary of the most frequently reported all-cause Grade 3-4 TEAEs (incidence of ≥2%) and drug-related Grade 3-4 TEAEs (incidence of ≥5%) in the NAPOLI-3 trial are presented in Table 10 and Table 11, respectively.
- 6.41 The resubmission contended that the PBAC's March 2024 conclusion was not appropriate and maintained that NALIRIFOX and Gem+NabP have different safety profiles and that, overall, it cannot be concluded that one safety profile is superior or inferior to the other. The resubmission stated that it was important to consider the spectrum of AEs in each of the arms of the NAPOLI-3 trial given the difference in AE profiles. Based on the Grade 3/4 TEAEs reported in the NAPOLI-3 trial (Table 10 and Table 11), there is a higher risk of diarrhoea, nausea, vomiting, mucosal inflammation, asthenia, decreased appetite, ≥20% body weight loss and hypokalaemia but there is a lower risk of anaemia, neutropenia, thrombocytopenia, leukopenia and decreased white blood cell count in the NALIRIFOX arm compared to the Gem+NabP arm. Gastrointestinal toxicity can impact quality of life, hydration and nutritional status and

³³ Jennifer J. Knox et al., Early results of the PASS-01 trial: Pancreatic adenocarcinoma signature stratification for treatment-01.. JCO 42, LBA4004-LBA4004(2024).

³⁴ www.vumedi.com/video/ascor-2024-insights-biomarker-directed-treatment-for-pancreatic-adenocarcinoma-early-results-from-th/

haematologic toxicity can lead to infections, fatigue and bleeding issues. Haematological toxicities and peripheral neuropathy often represent treatment-limiting adverse events³⁵.

- 6.42 It is acknowledged that NALIRIFOX and Gem+NabP have different AE profiles. However, gastrointestinal Grade 3-4 TEAEs, such as diarrhoea and vomiting, are likely to be more critical AEs that may require hospitalisations and impact on patient's quality-of-life compared to blood and lymphatic system Grade 3-4 TEAEs such as neutropenia and anaemia, which may not necessarily present symptoms and this will most likely be detected during regular screening/blood testing where patients can receive more timely treatment.

³⁵ Cooray, P., Zalberg, J. (2024). First-line treatments for metastatic pancreatic cancer: Overview of key trials shaping the treatment landscape in Australia. *Key Opinions in Medicine* (Ahead of print).

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Table 9: Summary of key adverse events in the NAPOLI-3 trial

AEs	NALIRIFOX N=370	Gem+NabP N=379	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n/N (%)	n/N (%)	OR and RR<1 favour NALIRIFOX		RD<0 favour NALIRIFOX
Any cause of TEAEs					
Any cause TEAEs	369/370 (99.73%)	376/379 (99.21%)	2.94 [0.30, 28.43]	1.01 [0.99, 1.02]	0.01 [-0.01, 0.02]
Grade ≥ 3 TEAEs	322/370 (87.03%)	326/379 (86.02%)	1.09 [0.72, 1.66]	1.01 [0.96, 1.07]	0.01 [-0.04, 0.06]
SAEs	201/370 (54.32%)	195/379 (51.45%)	1.12 [0.84, 1.50]	1.06 [0.92, 1.21]	0.03 [-0.04, 0.10]
TEAEs leading to treatment discontinuation	118/370 (31.89%)	112/379 (29.55%)	1.12 [0.82, 1.52]	1.08 [0.87, 1.34]	0.02 [-0.04, 0.09]
TEAEs leading to discontinuation of nal-IRI	63/370 (17.03%)	NA	NE	NE	NE
TEAEs leading to reduction of any IMP	208/370 (56.22%)	190/379 (50.13%)	1.28 [0.96, 1.70]	1.12 [0.98, 1.28]	0.06 [-0.01, 0.13]
TEAEs leading to reduction of nal-IRI	194/370 (52.43%)	NA	NE	NE	NE
TEAEs leading to interruption of any IMP	16/370 (4.32%)	4/379 (1.06%)	4.24 [1.40, 12.80]	4.10 [1.38, 12.14]	0.03 [0.01, 0.06]
TEAEs leading to interruption of nal-IRI	7/370 (1.89%)	NA	NE	NE	NE
TEAEs leading to death	22/370 (5.95%)	23/379 (6.07%)	0.98 [0.54, 1.79]	0.98 [0.56, 1.73]	0.00 [-0.04, 0.03]
Drug-related TEAEs					
Any Drug-related TEAEs	352/370 (95.14%)	352/379 (92.88%)	1.50 [0.81, 2.77]	1.02 [0.99, 1.06]	0.02 [-0.01, 0.06]
Drug-related Grade ≥ 3 TEAEs	262/370 (70.81%)	258/379 (68.07%)	1.14 [0.83, 1.55]	1.04 [0.95, 1.14]	0.03 [-0.04, 0.09]
Drug-related SAEs	98/370 (26.49%)	72/379 (19.00%)	1.54 [1.09, 2.17]	1.39 [1.07, 1.82]	0.07 [0.01, 0.13]
Drug-related TEAEs leading to treatment discontinuation	94/370 (25.41%)	88/379 (23.22%)	1.13 [0.81, 1.57]	1.09 [0.85, 1.41]	0.02 [-0.04, 0.08]
Drug-related TEAEs leading to discontinuation of nal-IRI	40/370 (10.81%)	NA	NE	NE	NE
Drug-related TEAEs leading to reduction of any IMP	198/370 (53.51%)	184/379 (48.55%)	1.22 [0.92, 1.63]	1.10 [0.96, 1.27]	0.05 [-0.02, 0.12]
Drug-related TEAEs leading to interruption of any IMP	12/370 (3.24%)	3/379 (0.79%)	4.20 [1.18, 15.01]	4.10 [1.17, 14.40]	0.02 [0.00, 0.04]
Drug-related TEAEs leading to death	6/370 (1.62%)	8/379 (2.11%)	0.76 [0.26, 2.22]	0.77 [0.27, 2.19]	0.00 [-0.02, 0.01]

Source: Table 33 (adapted), p76 of March 2024 submission.

Abbreviations; AE, adverse event; CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; IMP, investigational medicinal product; NA, not applicable; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NE, not evaluable; OR, odds ratio; RD, risk difference; RR, relative risk; SAE, serious adverse event; TEAE, treatment emergent adverse event.

Note: Results in **bold** indicate statistically significant difference (p < 0.05) based on post hoc analyses.

Blue shading indicates information previously seen by the PBAC.

Table 10: Summary of all-cause Grade 3-4 TEAEs with an incidence of ≥ 2% in the NAPOLI-3 trial (Safety Population)

AEs	NALIRIFOX	Gem+NabP	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n /N (%)	n /N (%)	OR and RR < 1 favours NALIRIFOX		RD < 0 favours NALIRIFOX
Any Grade 3-4 TEAEs	322/370 (87.03%)	326/379 (86.02%)	1.09 [0.72, 1.66]	1.01 [0.96, 1.07]	0.01 [-0.04, 0.06]
Gastrointestinal disorders					
Diarrhoea	75/370 (20.27%)	17/379 (4.49%)	5.41 [3.13, 9.37]	4.52 [2.72, 7.50]	0.16 [0.11, 0.20]
Nausea	44/370 (11.89%)	10/379 (2.64%)	4.98 [2.47, 10.06]	4.51 [2.30, 8.82]	0.09 [0.06, 0.13]
Vomiting	26/370 (7.03%)	8/379 (2.11%)	3.51 [1.57, 7.85]	3.33 [1.53, 7.26]	0.05 [0.02, 0.08]
General disorders and administration site conditions					
Fatigue	23/370 (6.22%)	20/379 (5.28%)	1.19 [0.64, 2.21]	1.18 [0.66, 2.11]	0.01 [-0.02, 0.04]
Asthenia	33/370 (8.92%)	19/379 (5.01%)	1.86 [1.04, 3.33]	1.78 [1.03, 3.07]	0.04 [0.00, 0.08]
Mucosal inflammation	8/370 (2.16%)	1/379 (0.26%)	8.35 [1.04, 67.13]	8.19 [1.03, 65.20]	0.02 [0.00, 0.03]
Blood and lymphatic system disorders					
Anaemia	39/370 (10.54%)	66/379 (17.41%)	0.56 [0.37, 0.85]	0.61 [0.42, 0.88]	-0.07 [-0.12, -0.02]
Neutropenia	52/370 (14.05%)	93/379 (24.54%)	0.50 [0.35, 0.73]	0.57 [0.42, 0.78]	-0.10 [-0.16, -0.05]
Thrombocytopenia	3/370 (0.81%)	14/379 (3.69%)	0.21 [0.06, 0.75]	0.22 [0.06, 0.76]	-0.03 [-0.05, -0.01]
Leukopenia	4/370 (1.08%)	17/379 (4.49%)	0.23 [0.08, 0.70]	0.24 [0.08, 0.71]	-0.03 [-0.06, -0.01]
Metabolism and nutrition disorders					
Decreased appetite	32/370 (8.65%)	10/379 (2.64%)	3.49 [1.69, 7.21]	3.28 [1.64, 6.57]	0.06 [0.03, 0.09]
Hypokalaemia	56/370 (15.14%)	15/379 (3.96%)	4.33 [2.40, 7.80]	3.82 [2.20, 6.64]	0.11 [0.07, 0.15]
Investigations					
Neutrophil count decreased	36/370 (9.73%)	51/379 (13.46%)	0.69 [0.44, 1.09]	0.72 [0.48, 1.08]	-0.04 [-0.08, 0.01]
Weight decreased	11/370 (2.97%)	1/379 (0.26%)	11.58 [1.49, 90.17]	11.27 [1.46, 86.84]	0.03 [0.01, 0.05]
White blood cell count decreased	6/370 (1.62%)	18/379 (4.75%)	0.33 [0.13, 0.84]	0.34 [0.14, 0.85]	-0.03 [-0.06, -0.01]
Nervous system disorders					
Neuropathy peripheral	12/370 (3.24%)	22/379 (5.80%)	0.54 [0.27, 1.12]	0.56 [0.28, 1.11]	-0.03 [-0.06, 0.00]

Source: Table 35, p81-82 of the March 2024 submission.

Abbreviations: AEs, adverse events; CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OR, odds ratio; RD, risk difference; RR, relative risk; TEAE, treatment emergent adverse event.

Note: Results in **bold** indicate statistically significant difference ($p < 0.05$) based on post hoc analyses.

Blue shading indicates information previously seen by the PBAC.

Table 11: Summary of most frequently reported drug-related Grade 3-4 TEAEs with an incidence of ≥ 5% (Safety Population).

AEs	NALIRIFOX N=370	Gem+NabP N=379	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n /N (%)	n /N (%)	OR and RR < 1 favours NALIRIFOX		RD < 0 favours NALIRIFOX
Any drug-related Grade 3-4 TEAEs	259/370 (70.00%)	255/379 (67.28%)	1.13 [0.83, 1.55]	1.04 [0.94, 1.15]	0.03 [-0.04, 0.09]
Gastrointestinal disorders					
Diarrhoea	72/370 (19.46%)	12/379 (3.17%)	7.39 [3.94, 13.87]	6.15 [3.39, 11.13]	0.16 [0.12, 0.21]
Nausea	42/370 (11.35%)	8/379 (2.11%)	5.94 [2.75, 12.83]	5.38 [2.56, 11.30]	0.09 [0.06, 0.13]
Vomiting	20/370 (5.41%)	5/379 (1.32%)	4.27 [1.59, 11.51]	4.10 [1.55, 10.80]	0.04 [0.02, 0.07]
General disorders and administration site conditions					
Fatigue	20/370 (5.41%)	14/379 (3.69%)	1.49 [0.74, 3.00]	1.46 [0.75, 2.85]	0.02 [-0.01, 0.05]
Asthenia	27/370 (7.30%)	14/379 (3.69%)	2.05 [1.06, 3.98]	1.98 [1.05, 3.71]	0.04 [0.00, 0.07]
Mucosal inflammation	7/370 (1.89%)	1/379 (0.26%)	7.29 [0.89, 59.54]	7.17 [0.89, 58.00]	0.02 [0.00, 0.03]
Nervous system disorders					
Neuropathy peripheral	12/370 (3.24%)	22/379 (5.80%)	0.54 [0.27, 1.12]	0.56 [0.28, 1.11]	-0.03 [-0.06, 0.00]
Blood and lymphatic system disorders					
Neutropenia	52/370 (14.05%)	88/379 (23.22%)	0.54 [0.37, 0.79]	0.61 [0.44, 0.83]	-0.09 [-0.15, -0.04]
Anaemia	27/370 (7.30%)	55/379 (14.51%)	0.46 [0.29, 0.75]	0.50 [0.32, 0.78]	-0.07 [-0.12, -0.03]
Thrombocytopenia	2/370 (0.54%)	13/379 (3.43%)	0.15 [0.03, 0.68]	0.16 [0.04, 0.69]	-0.03 [-0.05, -0.01]
Leukopenia	3/370 (0.81%)	17/379 (4.49%)	0.17 [0.05, 0.60]	0.18 [0.05, 0.61]	-0.04 [-0.06, -0.01]
Investigations					
Neutrophil count decreased	36/370 (9.73%)	50/379 (13.19%)	0.71 [0.45, 1.12]	0.74 [0.49, 1.10]	-0.03 [-0.08, 0.01]
WBC count decreased	6/370 (1.62%)	18/379 (4.75%)	0.33 [0.13, 0.84]	0.34 [0.14, 0.85]	-0.03 [-0.06, -0.01]
Metabolism and nutrition disorders					
Decreased appetite	24/370 (6.49%)	2/379 (0.53%)	13.08 [3.07, 55.73]	12.29 [2.93, 51.64]	0.06 [0.03, 0.09]
Hypokalaemia	27/370 (7.30%)	6/379 (1.58%)	4.89 [2.00, 12.00]	4.61 [1.93, 11.03]	0.06 [0.03, 0.09]

Source: Table 37, p87-88 of March 2024 submission.

Abbreviations; AE, adverse event; CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OR, odds ratio; RD, risk difference; RR, relative risk; TEAE, treatment emergent adverse event, WBC, white blood cell.

Note: Results in **bold** indicate statistically significant difference (p < 0.05) based on post hoc analyses.

Blue shading indicates information previously seen by the PBAC.

6.43 At March 2024 meeting, the PBAC considered that the claim of non-inferior comparative safety of NALIRIFOX versus Gem+NabP was not adequately supported by the data, due to increased rates of drug related serious adverse events, as well as all-

cause and drug-related TEAEs leading to interruption of treatment, for NALIRIFOX patients in NAPOLI-3 compared with Gem+NabP (para 7.9, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). The PBAC also noted that the safety profiles of NALIRIFOX and Gem+NabP were different. The PBAC considered that higher rates of gastrointestinal toxicities such as diarrhoea and nausea with NALIRIFOX would be significant for patients and impact quality of life (para 7.9, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).

- 6.44 The resubmission acknowledged that the safety profiles of the two regimens are different and that there is a higher risk of gastrointestinal disorders, asthenia, and hypokalaemia but also a lower risk of haematologic toxicity in the NALIRIFOX arm compared to the Gem+NabP arm. The resubmission stated that gastrointestinal toxicity can impact quality of life, hydration and nutritional status, and haematologic toxicity often represent treatment-limiting adverse events and can lead to infections, fatigue and bleeding issues. The resubmission argued that, in clinical practice, individual patient factors will determine which toxicity profile is likely to be most problematic for a patient. The PSCR suggested that NALIRIFOX may be preferred in patients who have a history of, or may be predisposed to, myelosuppression or peripheral neuropathy; and in patients who have received prior gemcitabine or radiation therapy.
- 6.45 Thus, the resubmission claimed that NALIRIFOX and Gem+NabP have different safety profiles but that, overall, it cannot be concluded that one safety profile is superior or inferior to the other. No additional safety data was presented in the resubmission to further support the safety claim. Previous concerns and limitations to safety data raised in the March 2024 PBAC meeting (see paragraph 6.44) remain.
- 6.46 The PSCR reiterated the PBAC has previously acknowledged the safety profiles of the two regimens are different, and there is a higher risk of gastrointestinal disorders, asthenia, and hypokalaemia associated with NALIRIFOX but lower risk of haematologic toxicity and potentially neuropathy compared to Gem+NabP. The PSCR also argued the determination as to which AE profile will be better or worse tolerated for an individual patient is made on a case by case basis in clinical practice. The ESC acknowledged these decisions are made individually, however agreed with the evaluation and considered that in practice, gastrointestinal disorders tended to be the types of events most likely to lead to hospitalisation, with associated impacts on quality of life.

NALIRIFOX versus FOLFIRINOX

- 6.47 Table 12 presents an ITC of the incidence of Grade ≥ 3 AEs reported in the GENERATE and NAPOLI-3 trials which was newly presented in the resubmission.

Table 12: ITC of incidence of Grade ≥3 AEs reported in the GENERATE and NAPOLI-3 trials

Adverse event	NAPOLI-3			GENERATE			NALIRIFOX vs mFOLFIRINOX (95% CI)
	NALIRIFOX N = 383	Gem+NabP N = 387	RR (95% CI)	mFOLFIRINOX N = 171	Gem+NabP N = 174	RR (95% CI)	
Gastrointestinal disorders							
Diarrhoea	75/370 (20.3%)	17/379 (4.5%)	4.52 (2.72, 7.50)	15/171 (8.8%)	2/174 (1.1%)	7.63 (1.77, 32.87)	0.59 (0.13, 2.78)
Nausea	44/370 (11.9%)	10/379 (2.6%)	4.51 (2.30, 8.82)	15/171 (8.8%)	4/174 (2.3%)	3.82 (1.29, 11.26)	1.18 (0.33, 4.22)
Anorexia	NR	NR	NC	22.8%	5.2%	NC	NC
General disorders and administration site conditions							
Fatigue	23/370 (6.2%)	20/379 (5.3%)	1.18 (0.66, 2.11)	7/171 (4.1%)	5/174 (2.9%)	1.42 (0.46, 4.40)	0.83 (0.23, 2.96)
Blood and lymphatic system disorders							
Anaemia	39/370 (10.5%)	66/379 (17.4%)	0.61 (0.42, 0.88)	18/171 (10.5%)	19/174 (10.9%)	0.96 (0.52, 1.77)	0.64 (0.31, 1.30)
Neutropenia	52/370 (14.1%)	93/379 (24.5%)	0.57 (0.42, 0.78)	88/171 (51.5%)	105/174 (60.3%)	0.85 (0.71, 1.03)	0.67 (0.47, 0.96)
Thrombocytopenia	3/370 (0.8%)	14/379 (3.7%)	0.22 (0.06, 0.76)	8/171 (4.7%)	8/174 (4.6%)	1.01 (0.39, 2.65)	0.22 (0.04, 1.07)
Febrile neutropenia	9/370 (2.4%)	9/379 (2.4%)	1.02 (0.41, 2.55)	15/171 (8.8%)	6/174 (3.4%)	2.54 (1.01, 6.40)	0.40 (0.11, 1.47)
Investigations							
Reduction in WBC	6/370 (1.6%)	18/379 (4.7%)	0.34 (0.14, 0.85)	38/171 (22.2%)	60/174 (34.5%)	0.64 (0.46, 0.91)	0.53 (0.20, 1.39)
ALT increased	13/370 (3.5%)	12/379 (3.2%)	0.95 (0.44, 2.05)	20/171 (11.7%)	19/174 (10.9%)	1.07 (0.59, 1.93)	0.89 (0.34, 2.35)
AST increased	11/370 (3.0%)	8/379 (2.1%)	1.41 (0.57, 3.46)	16/171 (9.4%)	14/174 (8.1%)	1.16 (0.59, 2.31)	1.22 (0.39, 3.77)
Nervous system disorders							
Neuropathy (peripheral)	12/370 (3.2%)	22/379 (5.8%)	0.56 (0.28, 1.11)	14/171 (8.2%)	19/174 (10.9%)	0.75 (0.39, 1.45)	0.75 (0.29, 1.93)
Infections (and infestations)							
Infections	34/370 (9.2%)	60/379 (15.8%)	0.58 (0.39, 0.86)	28/174 (16.4%)	19/174 (10.9%)	1.50 (0.87, 2.58)	0.39 (0.20, 0.76)

Source: Table 2.11, p45-46 of resubmission.

Abbreviations: AEs, adverse events; ALT, Alanine transaminase; AST, Aspartate transaminase; CI, confidence interval; FOLFIRINOX, 5-fluorouracil, leucovorin/folinic acid, standard irinotecan, and oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; ; ITC, indirect treatment comparison; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NC, not calculable; NR, not reported; RR, relative risk; WBC, white blood cell.

Note: Results in **bold** indicate significant difference.

6.48 The resubmission stated that both NALIRIFOX and mFOLFIRINOX are associated with a higher incidence of gastrointestinal AEs compared to Gem+NabP. NALIRIFOX was associated with a lower incidence of haematological AEs compared to Gem+NabP, and mFOLFIRINOX was generally similar to Gem+NabP in terms of these AEs, except for neutropenia and febrile neutropenia.

6.49 Based on the ITC analysis, the resubmission stated that NALIRIFOX appears to be associated with significantly lower AEs than mFOLFIRINOX for neutropenia and infections. The resubmission noted this was despite the use of a mFOLFIRINOX regimen in GENERATE that incorporated a reduced dose of irinotecan and omitted the bolus 5-FU dose (compared to the FOLFIRINOX regimen endorsed by eviQ) to reduce

the frequency of severe toxicities. No significant differences were found in other AEs reported. Results should be interpreted with caution noting the potential transitivity issues described in paragraph 6.35 across these trials and the low numbers of some adverse event types. These results differed from the NALIRIFOX vs FOLFIRINOX comparisons presented in Nichetti et al. (2024) which reported statistically significant differences in platelet count decreases (OR=5.13; 95% CI 1.78, 14.77) and vomiting (OR=0.45; 95% CI 0.25, 0.81) and not statistically significantly different for neutrophil count decrease (OR=0.66; 95% 0.28, 1.55).

Benefits/harms

NALIRIFOX versus Gem+NabP

6.50 A summary of the comparative benefits and harms of NALIRIFOX versus Gem+NabP is presented in Table 13.

Table 13: Summary of comparative benefits and harms for NALIRIFOX and Gem+NabP

Event	NALIRIFOX n (%)	Gem+NabP n (%)	Absolute Difference	HR (95% CI) ^a		
BENEFITS						
Overall survival (median duration of follow up 29.5 months)						
Deaths, n/N (%)	328 (85.6)	345 (89.1)	-	0.84 (0.72, 0.98) p=0.026		
Median OS, months (95% CI)	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)	1.9			
% Alive at 3 months (95% CI)	NR	NR	1.7%			
% Alive at 6 months (95% CI)	72.4 (67.6, 76.6)	68.4 (63.5, 72.8)	4.0%			
% Alive at 9 months (95% CI)	58.1 (53.0, 62.9)	51.8 (46.7, 56.7)	6.3%			
% Alive at 12 months (95% CI)	45.6 (40.5, 50.5)	39.6 (34.7, 44.5)	6.0%			
% Alive at 18 months (95% CI)	26.6 (22.2, 31.1)	20.0 (16.1, 24.1)	6.6%			
Overall survival (median duration of follow up 16.0 months in NALIRIFOX and 16.3 months in Gem+NabP)						
Deaths, n/N (%)	259/383 (67.6)	285/387 (73.6)	-	0.83 (0.70, 0.99) p=0.04		
Median OS, months (95% CI)	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)	1.9			
% Alive at 3 months (95% CI)	84.2 (80.2, 87.5)	82.5 (78.3, 86.0)	1.7%			
% Alive at 6 months (95% CI)	72.4 (67.6, 76.6)	68.4 (63.5, 72.8)	4%			
% Alive at 9 months (95% CI)	58.1 (53.0, 62.9)	51.8 (46.7, 56.7)	6.3%			
% Alive at 12 months (95% CI)	45.6 (40.5, 50.5)	39.5 (34.6, 44.4)	6.1%			
% Alive at 18 months (95% CI)	26.2 (20.9, 31.7)	19.3 (14.8, 24.2)	6.9%			
Progression free survival (median duration of follow up 16.1 months)						
Progressed, n (%)	249/383 (65.0)	259/387 (66.9)	-	0.69 (0.58, 0.83) p<0.0001		
Median PFS, months (95% CI)	7.4 (6.0, 7.7)	5.6 (5.3, 5.8)	1.8			
% not progressed at 3 months (95% CI)	76.9 (72.1, 81.1)	71.5 (66.5, 75.9)	5.4%			
% not progressed at 6 months (95% CI)	56.4 (50.7, 61.6)	43.2 (37.6, 48.6)	13.2%			
% not progressed at 9 months (95% CI)	40.9 (35.3, 46.4)	24.9 (19.8, 30.2)	16.0%			
% not progressed at 12 months (95% CI)	27.4 (22.3, 32.7)	13.9 (9.7, 18.9)	13.5%			
% not progressed at 18 months (95% CI)	11.4 (7.1, 16.9)	3.6 (0.5, 12.3)	7.8%			
HARMS (Grade 3-4)						
	N=370	N=379	RR (95% CI)	Event rate/100 patients	RD (95% CI)	
				NALIRIFOX	Gem+NabP	
Diarrhoea	75	17	4.52 [2.72, 7.50]	20.3	4.5	0.16 [0.11, 0.20]
Hypokalaemia	56	15	3.82 [2.20, 6.64]	15.1	4.0	0.11 [0.07, 0.15]
Nausea	44	10	4.51 [2.30, 8.82]	11.9	2.6	0.09 [0.06, 0.13]
Decreased appetite	32	10	3.28	8.7	2.6	0.06

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Event		NALIRIFOX n (%)		Gem+NabP n (%)	Absolute Difference	HR (95% CI) ^a
BENEFITS		N=383		N=387		
			[1.64, 6.57]			[0.03, 0.09]
Vomiting	26	8	3.33 [1.53, 7.26]	7.0	2.1	0.05 [0.02, 0.08]
Asthenia	33	19	1.78 [1.03, 3.07]	8.9	5.0	0.04 [0.00, 0.08]
Weight decreased	11	1	11.27 [1.46, 86.84]	3.0	0.3	0.03 [0.01, 0.05]
Mucosal inflammation	8	1	8.19 [1.03, 65.20]	2.2	0.3	0.02 [0.00, 0.03]
Dehydration	12	4	3.07 [1.00, 9.44]	3.2	1.1	0.02 [0.00, 0.04]
Neutropenia	52	93	0.57 [0.42, 0.78]	14.1	24.5	-0.10 [-0.16, -0.05]
Anaemia	39	66	0.61 [0.42, 0.88]	10.5	17.4	-0.07 [-0.12, -0.02]
Thrombocytopenia	3	14	0.22 [0.06, 0.76]	0.8	3.7	-0.03 [-0.05, -0.01]
Leukopenia	4	17	0.24 [0.08, 0.71]	1.1	4.5	-0.03 [-0.06, -0.01]
White blood cell decreased	6	18	0.34 [0.14, 0.85]	1.6	4.8	-0.03 [-0.06, -0.01]

Source: Table 2.4, Table 2.6, pp21-23 of resubmission, and Table 35, p81-82 of March 2024 submission.

Abbreviations: CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NR, not reported; OS, overall survival; PFS, progression free survival; RD, risk difference; RR, risk ratio.

^a Hazard ratio and 95% CI stratified by ECOG performance status (0/1), region (North America/East Asia/Rest of the world), and liver metastases (Yes/No). A hazard ratio <1 indicates an advantage for NALIRIFOX.

Note: Results in **bold** indicate statistically significant difference (p < 0.05).

Blue shading indicates information previously seen by the PBAC.

6.51 On the basis of direct comparison evidence presented by the resubmission, the comparison of NALIRIFOX and Gem+NabP resulted in improvements of approximately 1.9 months in median OS over a median duration of follow-up of 29.5 months and improvement of 1.8 months in median PFS over a median duration of follow-up of 16.1 months.

6.52 The resubmission claimed that NALIRIFOX has a different safety profile compared to Gem+NabP (neither superior nor inferior). On the basis of direct comparison evidence presented by the resubmission, for every 100 patients treated with NALIRIFOX in comparison to Gem+NabP:

- Approximately additional 15 patients would experience a grade 3 or 4 diarrhoea.
- Approximately additional 11 patients would experience a grade 3 or 4 hypokalaemia.
- Approximately additional 9 patients would experience a grade 3 or 4 nausea in which hospitalisation may be indicated.
- Approximately additional 6 patients would experience a grade 3 or 4 decreased appetite which may result in significant weight loss or malnutrition.

- Approximately additional 5 patients would experience a grade 3 or 4 vomiting in which hospitalisation may be indicated.
- Approximately additional 4 patients would experience a grade 3 or 4 asthenia.
- Approximately additional 3 patients would experience a grade 3 or 4 weight loss or more than 20% from baseline.
- Approximately additional 2 patients would experience a grade 3 or 4 mucosal inflammation.
- Approximately additional 2 patients would experience a grade 3 or 4 dehydration.
- Approximately 10 fewer patients would experience a grade 3 or 4 neutropenia.
- Approximately 6 fewer patients would experience a grade 3 or 4 anaemia.
- Approximately 3 fewer patients would experience a grade 3 or 4 thrombocytopenia.
- Approximately 3 fewer patients would experience a grade 3 or 4 leukopenia.
- Approximately 3 fewer patients would experience a grade 3 or 4 decrease in white blood cells.

NALIRIFOX versus FOLFIRINOX

6.53 The indirect treatment comparison presented in the resubmission did not allow for a robust comparison of benefits and harms of NALIRIFOX versus FOLFIRINOX given the concerns raised by PBAC (para 6.10) and limitations of the ITC results (para 6.35). Accordingly, a benefits/harms table has not been presented.

Clinical claim

NALIRIFOX versus Gem+NabP

- 6.54 The resubmission described NALIRIFOX as superior in terms of effectiveness and non-inferior/non-superior in terms of safety compared to Gem+NabP based on the direct comparison from NAPOLI-3.
- 6.55 Despite the availability of longer follow-up OS data up to 29.5 months (increased from 16.1 months in the March 2024 submission), the improvement in median OS observed in NALIRIFOX over Gem+NabP remains at 1.9 months, the same as reported in the previous submission. The PBAC considered the magnitude was small and may not be clinically meaningful (para 7.8, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).
- 6.56 The evaluation considered the therapeutic conclusion for safety was not adequately supported because the resubmission did not provide sufficient evidence to address the PBAC's previous concerns. Although it is acknowledged that the AE profiles are different, previous concerns and limitations to safety data raised by the PBAC in the March 2024 meeting remain (increased rates of drug-related serious adverse events, as well as all-cause and drug-related TEAEs leading to interruption of treatment for

NALIRIFOX patients in NAPOLI-3 compared with Gem+NabP; para 7.9, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).

- 6.57 The PBAC noted limited new data were submitted with respect to the comparative effectiveness of NALIRIFOX and Gem+NabP, and the resubmission reported no difference in median overall survival compared to the original submission. On that basis, the PBAC reaffirmed its previously expressed view that the claim of superior comparative effectiveness was supported by the available data, but the benefits in terms of OS remained small and may not be clinically meaningful.
- 6.58 The PBAC considered the claim of non-inferior/non-superior comparative safety of NALIRIFOX and Gem+NabP was not adequately supported, as whilst the safety profiles of NALIRIFOX and Gem+NabP are different (paragraph 6.53 refers), the types of adverse events associated with NALIRIFOX are more likely to require hospitalisation and have greater impacts on quality of life.

NALIRIFOX versus FOLFIRINOX

- 6.59 Based on the evidence from the ITCs of NALIRIFOX vs FOLFIRINOX using data from the NAPOLI-3 and GENERATE trials, the resubmission claimed that NALIRIFOX is superior in terms of effectiveness and appears to have advantages over the FOLFIRINOX regimen in terms of the incidence of haematological adverse events, including the sequelae of those events (e.g., infection).
- 6.60 The therapeutic conclusion presented in the resubmission for effectiveness and safety is not adequately supported by the indirect evidence presented in the resubmission because:
- Previous concerns of the GENERATE trial raised by the PBAC in March 2024 meeting regarding comparability, high discontinuation rates and inadequate reporting (para 6.10) and 6.31) remain valid and unresolved by the additional information presented.
 - The results of the MAIC and the single-step ITCs for effectiveness and safety should be interpreted with caution given the concerns of risk of bias and differences between the NAPOLI-3 and GENERATE trials (paras 6.14 and 6.32). Both ITCs were based on limited clinical evidence of the GENERATE trial (abstract and ESMO presentation slides) that has limited supporting information available.
 - Despite the adjustments to reweight the population from the NAPOLI-3 trial to match those in the GENERATE trial to conduct a MAIC, the analysis was not able to account for all differences in baseline characteristics thus limited by the possibility of residual confounding.
 - Overall, when accounting for these issues and uncertainties, the assumption of transitivity was likely violated for the comparison of NALIRIFOX and mFOLFIRINOX using the data from the GENERATE study; therefore, the ITCs could not be considered robust.

- 6.61 A large body of evidence for comparative effectiveness was not included in the resubmission, resulting in a different conclusion to that made in the March 2024 submission. The results of the single-step ITC and MAIC presented in the resubmission also differed from the results of the multistep ITC and Nichetti et al (2024) presented in the March 2024 PBAC meeting, which suggested no statistically significant difference between NALIRIFOX and FOLFIRINOX for OS and PFS (Table 8).
- 6.62 The PBAC considered the claim of superior comparative effectiveness and appearing to 'have advantages' over FOLFIRINOX was not adequately supported, as the GENERATE trial was not sufficiently exchangeable with the other presented evidence, was likely not applicable to the Australian context, and there was limited information available about the trial (6.31). Therefore, the PBAC considered the comparisons using the GENERATE trial were not robust and further considered the other available analyses did not support the claims made in the resubmission.

Economic analysis

- 6.63 The resubmission presented a stepped economic evaluation comparing NALIRIFOX to a mixed comparator of Gem+NabP (75%) and FOLFIRINOX (25%), based on the direct randomised trial, NAPOLI-3 (NALIRIFOX vs Gem+NabP), and the MAIC of NALIRIFOX vs FOLFIRINOX which used data from the NAPOLI-3 and GENERATE (FOLFIRINOX vs Gem+NabP) trials. The type of economic evaluation presented was a cost-utility analysis.
- 6.64 The ESC considered the economic analysis approach taken by the resubmission to be inappropriate. Noting its view that FOLFIRINOX was the appropriate comparator and that a claim of superior comparative effectiveness and safety for NALIRIFOX over FOLFIRINOX was not adequately supported, the ESC agreed with the view previously expressed by the PBAC, that the appropriate form of economic evaluation would be a cost minimisation approach (para 7.15, irinotecan (nanoliposomal) PSD, March 2024 PBAC meeting).
- 6.65 The proportions of the mixed comparator were informed by the market share of first-line treatments for Australian patients with mPAC captured in the PURPLE registry (85.1% Gem+NabP, 14.9% FOLFIRINOX) and assumptions of substitution of these treatments by NALIRIFOX (up to 10% of the Gem+NabP market and up to 10% of the FOLFIRINOX market). The evaluation noted there is considerable uncertainty in the proposed mixed comparator split. The PBAC previously determined that FOLFIRINOX was the relevant main comparator in the proposed population, rather than Gem+NabP (para 7.1, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting). The proportions of the mixed comparator are a key driver of the incremental cost-effectiveness ratio (ICER) in the economic evaluation.
- 6.66 A summary of the key components of the economic evaluation is presented in Table 14.

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Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	NALIRIFOX vs mixed comparator (75% Gem+NabP/25% FOLFIRINOX)
Time horizon	5 years (60 months) in the model base case vs. 29.5 months (median follow-up) in the key trial (NAPOLI-3)
Discounting	5% per annum (applied to outcomes and end-of-life costs) Drug and drug administration costs, costs of subsequent therapies and costs of treating AEs were applied as a one-off cost at the start of the model, therefore not discounted.
Outcomes	Life years gained, QALYs gained
Health states	Free of progression Progressed Dead
Methods used to generate results	Partitioned survival analysis model. The model was informed by PFS and OS time-to-event data from the NAPOLI-3 trial (for NALIRIFOX and Gem+NabP) and HRs from the MAIC of NALIRIFOX vs FOLFIRINOX (for FOLFIRINOX) which determined the distribution of patients across the three health states. The resubmission included more favourable estimates for the comparative effectiveness of NALIRIFOX vs FOLFIRINOX compared with the March 2024 submission, which the ESC considered was not appropriate as it relied on data from the GENERATE trial to inform the ITC.
Extrapolation method	OS and PFS KM data from the NAPOLI-3 trial were truncated at selected time points where 10% of patients remain at risk. Parametric models were fit to the data from these time points and extrapolated over the 5-year time horizon. The selection for best fitting curves was based on AIC and BIC assessments. The submission assumed a constant and continuous treatment effect for both endpoints (assuming proportional hazards assumptions were met). 17% of QALYs and 7% of costs occur in the extrapolated period in the NALIRIFOX arm and 13% of QALYs and 6% of costs occur in the extrapolated period in the mixed comparator arm.
Cycle length	28 days
Health state utility values	EQ-5D-5L data (using UK value set) from the NAPOLI-3 trial (Free of Progression=0.85, Progressed=0.78). Sensitivity analysis undertaken using AU value set for EQ-5D-5L data from NAPOLI-3 trial (Free of Progression=0.89, Progressed=0.82).
First-line drug costs	Based on patient-level data from treatment regimens administered to patients in the NAPOLI-3 (NALIRIFOX and Gem+NabP) and ACCORD11/PRODIGE4 (FOLFIRINOX) trials. The resubmission applies a reduced dose of Leucovorin/Folinic acid of 50 mg flat (compared to 400 mg/m ² as was used in the NAPOLI-3 and ACCORD11/PRODIGE4 trials). The resubmission applied a rebate of ■■■% on government expenditure of nal-IRI (increased from a ■■■% rebate proposed in the March 2024 submission) and assumed a 40% rebate on government expenditure of NabP in the economic model (no rebate was applied for NabP in the March 2024 submission).
Drug administration costs	A chemotherapy administration fee based on MBS item 13950 is applied for each administration of each regimen over the course of treatment.
Costs related to subsequent anticancer therapy	Current PBS restriction does not allow for the use of NabP second- or subsequent-line and nal-IRI is not PBS-listed; therefore, the submission applied the lower cost PBS-listed paclitaxel and irinotecan as substitutes, and actual costs of these medications were tested in sensitivity analysis.
Costs related to AE management	Costs associated with management of Grade 3-4 treatment emergent adverse events (TEAEs) were included in the economic evaluation, informed by incidence rates derived from the NAPOLI-3 trial (for NALIRIFOX and Gem+NabP) and GENERATE (for FOLFIRINOX).

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Component	Summary
	Clinician advice was sought to inform the management of TEAEs and these were costed in accordance with the recommendations of the PBAC Manual of Resource Items and their Associated Costs.

Source: Compiled during the evaluation.

Abbreviations: AEs, adverse events; AIC, Akaike Information Criterion; AU, Australia; BIC, Bayesian Information Criterion; EQ-5D-5L, EuroQol 5-dimension health status questionnaire (5 level); FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching adjusted indirect treatment comparison; MBS, Medicare Benefits Schedule; NabP, nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, nanoliposomal irinotecan in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; TEAE, treatment emergent adverse event; UK, United Kingdom.

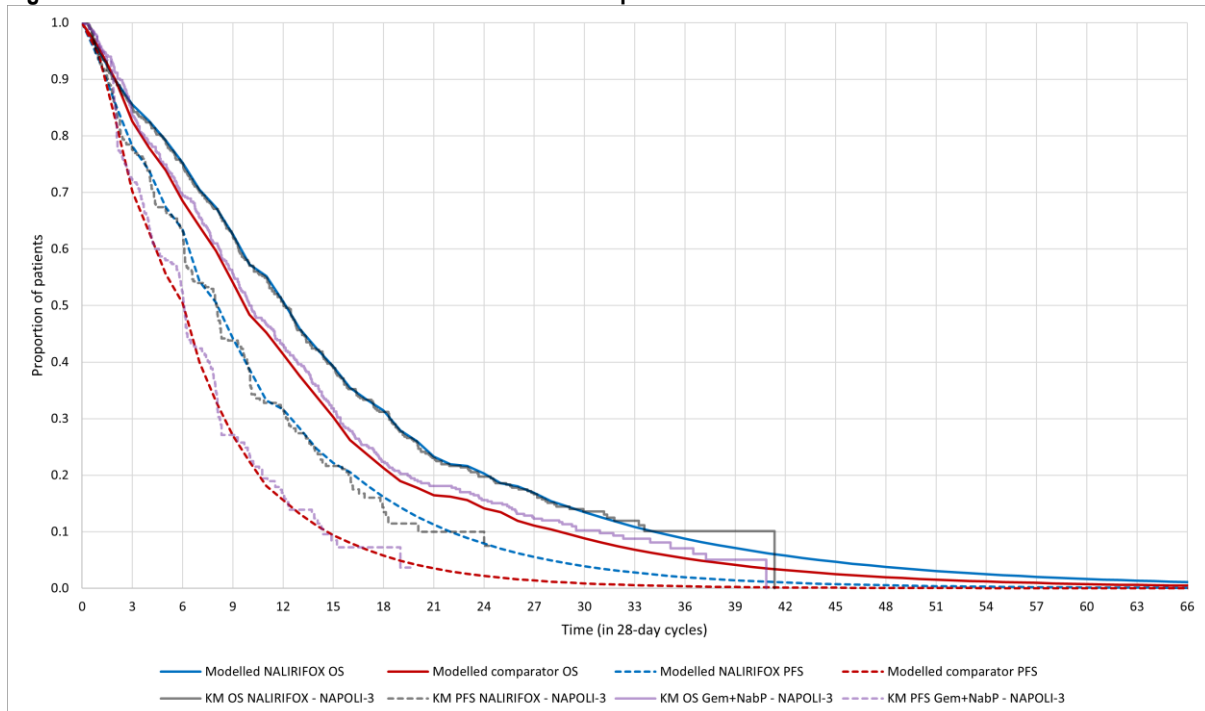
Blue shading indicates these elements were unchanged from the March 2024 submission.

- 6.67 The economic model used a partitioned-survival model, with the results calculated using an expected value analysis, with results reported for a single average patient.
- 6.68 The resubmission used PFS and OS curves from the NAPOLI-3 trial to inform the proportion of patients and time spent in each of the health states in the economic model for the NALIRIFOX and Gem+NabP treatment arms. For the FOLFIRINOX treatment arm, HRs from the MAIC of NALIRIFOX vs FOLFIRINOX were applied to NALIRIFOX PFS and OS curves (OS HR=0.66 (95%CI 0.47, 0.92) and PFS HR=0.53 (0.39, 0.72)). This differs from the March 2024 submission which modelled two alternative scenarios that were more conservative with respect to the comparative effectiveness of NALIRIFOX and FOLFIRINOX. The resubmission used more favourable estimates for the comparative effectiveness of NALIRIFOX vs FOLFIRINOX compared to the March 2024 submission.
- 6.69 The availability of additional OS follow-up data from the NAPOLI-3 trial has resulted in new extrapolations for NALIRIFOX and Gem+NabP OS in the resubmission. The extrapolation and modelled curves for PFS from NAPOLI-3 have not changed from the March 2024 submission as no additional PFS data have been reported (PFS HR applied was 0.69 (95%CI 0.58,0.83)).
- 6.70 Consistent with the March 2024 submission, the Weibull function was used to extrapolate NALIRIFOX and Gem+NabP OS curves beyond the observed data as it was statistically the best-fitting parametric function according to both the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
- 6.71 Consistent with the March 2024 submission, the point at which KM data switches to extrapolated data in the base-case economic analysis was informed by the publication by Pocock et al, 2002. The PBAC previously determined that the approach used by Pocock et al, 2002, with OS and PFS KM functions used for 19 cycles/16 cycles for NALIRIFOX and 18 cycles/11 cycles for Gem+NabP, resulted in the exclusion of a substantial number of patients (77 out of 770 patients in the NAPOLI-3 trial) from the base case analysis. The ICER was sensitive to the time point selected for extrapolation, however, given the updated NAPOLI-3 OS data available in the resubmission, the revised time point switch from OS/PFS KM data to extrapolation is now 29 cycles/16 cycles in the NALIRIFOX arm and 28 cycles/11 cycles in the Gem+NabP

arm. The ICER in the resubmission is not sensitive to alternative timepoints of 1% and 2%.

6.72 Modelled PFS and OS curves for NALIRIFOX and Gem+NabP, compared to KM data derived from NAPOLI-3 are presented in Figure 3.

Figure 3: Modelled NALIRIFOX and Gem+NabP curves compared to KM data from NAPOLI-3



Source: Sheet 'Results' of the economic workbook.

Abbreviations: Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; KM, Kaplan-Meier; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; OS, overall survival; PFS, progression-free survival.

Note: The term comparator refers to Gem+NabP only

6.73 Health state utility values derived from the NAPOLI-3 trial, based on the United Kingdom EQ-5D-5L value set, were applied to both the NALIRIFOX and comparator arms in the base case economic analysis. This was unchanged from the March 2024 submission. The ESC previously noted these values, which were unpublished and not able to be externally verified, were higher than those available from the literature and were an important driver of the ICER. However, the ESC considered the use of trial-based utilities to be appropriate (para 6.80, irinotecan (nanoliposomal), PSD, March 2024 PBAC meeting).

6.74 Consistent with the March 2024 submission, the costs of first-line drug and administration costs were based on regimens administered to patients in the NAPOLI-3 (NALIRIFOX and Gem+NabP) and ACCORD11/PRODIGE4 (FOLFIRINOX) trials. However, the median duration of treatment from the GENERATE trial was applied to determine costs for the FOLFIRINOX treatment arm in the base case. The ICER is moderately sensitive to using the median duration of treatment from the ACCROD11/PRODIGE4 trial (+1%). Additionally, there is a mismatch between the

source of data informing the effectiveness (GENERATE) and costs (ACCORD11/PRODIGE4) of FOLFIRINOX in the economic model which adds uncertainty to the results.

- 6.75 Patient-level data on drug exposure was available from these trials and was used to determine the average number of vials that would be dispensed for each administration of each drug in each treatment regimen, which was unchanged from the original submission.
- 6.76 The costs of the medications were based on updated PBS-listed AEMPs for each of the respective medications, adjusted to efficient funding of chemotherapy (EFC) public hospital and private hospital fees and weighted based on the split of nanoparticle albumin-bound paclitaxel (NabP) prescriptions processed for mPAC between August 2022 and July 2023 (28% public and 72% private). The effective DPMA of nal-IRI used in the economic model was \$| (public) and \$| (private). The resubmission assumed a 40% rebate on NabP in the economic model (no rebate was applied for NabP in base case in the March 2024 submission but different percentages were presented in sensitivity analyses).
- 6.77 Consistent with the March 2024 submission, costs of subsequent systemic anticancer therapies as reported in the NAPOLI-3 trial (used by at least 2% of patients in either treatment arm) were included in the economic evaluation. Subsequent therapies in NAPOLI-3 included the use of Gem+NabP, NabP monotherapy and nal-IRI. A sensitivity analysis applying costs as per the subsequent therapies used in the NAPOLI-3 trial was undertaken during the evaluation; however the ICER was not sensitive to this input.
- 6.78 Costs associated with management of Grade 3-4 TEAEs were included in the economic evaluation, informed by incidence rates derived from the NAPOLI-3 trial (for NALIRIFOX and Gem+NabP). For FOLFIRINOX, the relative risk of each TEAE for FOLFIRINOX vs Gem+NabP was derived from the GENERATE trial and applied to the observed incidence of the TEAE in the Gem+NabP arm of the NAPOLI-3 trial. If an event was not reported, incidence as per the NALIRIFOX arm of the NAPOLI-3 was applied.
- 6.79 The resubmission assumed that 100% of patients with grade 3/4 diarrhoea are hospitalized (applying costs associated diagnosis related group (DRG) G67 – consistent with ESC recommendations from the March 2024 submission) and 50% of patients with grade 3/4 mucosal inflammation are hospitalized (applying costs associated with DRG G70- not consistent with ESC recommendations from the March 2024 submission). A sensitivity analysis applying the costs of managing mucosal inflammation recommended by the ESC in the March 2024 submission (= \$13,283.46, based on DRG G03C and assuming 100% of patients are hospitalized) was undertaken in the evaluation; this increased the ICER slightly (+|% from base case).
- 6.80 A summary of the key drivers of the model is presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: \$ [redacted] /QALY gained.
Comparative effectiveness of NALIRIFOX vs FOLFIRINOX	HRs from the MAIC of NALIRIFOX vs FOLFIRINOX PFS HR (95% CI): 0.53 (0.39, 0.72) OS HR (95% CI): 0.66 (0.47, 0.92)	High, favours NALIRIFOX Assuming FOLFIRINOX is non-inferior to Gem+NabP increased the ICER to \$ [redacted] /QALY gained (+ [redacted] %). Assuming NALIRIFOX is non-inferior to FOLFIRINOX increase the ICER to \$ [redacted] /QALY gained (+ [redacted] %).
Proportions of mixed comparator	Based on analysis of current market share of treatments in Australian patients with mPAC from the PURPLE registry (85.1% Gem+NabP/14.9% FOLFIRINOX) and assumptions of extent of substitution by NALIRIFOX ([redacted] % of Gem+NabP market and [redacted] % of FOLFIRINOX market). Proportions of mixed comparator in base case is 75% Gem+NabP/25% FOLFIRINOX	High, favours mixed comparator if clinical claim of superiority of NALIRIFOX vs FOLFIRINOX is accepted. Use of mixed comparator proportions 50% Gem+NabP/50% FOLFIRINOX decreased the ICER to \$ [redacted] /QALY gained (- [redacted] %) Use of mixed comparator proportions 0% Gem+NabP/100% FOLFIRINOX decreased the ICER to \$ [redacted] /QALY gained (- [redacted] %) If clinical claim of superiority of NALIRIFOX vs FOLFIRINOX is not accepted (assume non-inferiority of FOLFIRINOX vs NALIRIFOX), favours NALIRIFOX. Use of mixed comparator proportions 50% Gem+NabP/50% FOLFIRINOX increased the ICER to \$ [redacted] /QALY gained (+ [redacted] %)
Utilities	EQ-5D-5L data (using UK value set) from the NAPOLI-3 trial (Free of Progression=0.85, Progressed=0.78).	High, favours NALIRIFOX Use of utility values from SEIGE trial (Free of Progression=0.70, Progressed=0.65) increased the ICER to \$ [redacted] /QALY gained (+ [redacted] %) Use of utility values from Romanus 2012 (Free of Progression=0.74, Progressed=0.67) increased the ICER to \$ [redacted] /QALY gained (+ [redacted] %)

Source: Compiled during the evaluation.

Abbreviations: EQ-5D-5L, EuroQol 5-dimension health status questionnaire (5 level); FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratios; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect treatment comparison; NALIRIFOX, nanoliposomal irinotecan in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; OS, overall survival; PURPLE, Pancreatic cancer: Understanding Routine Practice & Lifting End registry; QALY, quality-adjusted life year.

Blue shading indicates these elements were unchanged from the March 2024 submission

Note: The SEIGE trial was a Phase II, dose-scheduling trial of Gem+NabP with EQ-5D-5L data captured over a period of 12 months.

Romanus et al, 2012 was a health-related quality of life study of US patients with advanced pancreatic cancer deemed not appropriate for surgical resection. Utility values adjusted to the UK population were from NICE's assessment of Gem+NabP.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

⁴ \$35,000 to < \$45,000

⁵ \$25,000 to < \$35,000

⁶ \$135,000 to < \$155,000

6.81 The use of HRs based on the resubmission ITCs using GENERATE leads to highly questionable model outputs, where the ICER decreases as the proportion of FOLFIRINOX use increases. Compared to the previous submission, the updated OS data from the NAPOLI-3 trial in the resubmission has resulted in the extrapolation time point and parametric function for OS no longer being key drivers of the model.

6.82 The results of the stepped economic evaluation are presented in Table 16.

Table 16: Results of the stepped economic evaluation

Step and component	NALIRIFOX	Comparator (75% Gem+NabP/25% FOLFIRINOX)	Increment
Step 1: trial-based costs and outcomes			
Costs	\$	\$	\$
LYs gained	1.1464	0.9566	0.1897
Incremental cost/extra LY gained			\$ ¹
Step 2: time horizon extended to 5 years, end-of-life costs added and discounting (5%) applied			
Costs	\$	\$	\$
LYs gained	1.1459	0.9533	0.1926
Incremental cost/extra LY gained			\$ ²
Step 3: utility weights applied			
Costs	\$	\$	\$
QALYs gained	0.9460	0.7802	0.1658
Incremental cost/extra QALY gained			\$ ¹
Base case – March 2024 submission ^a			
Costs	\$	\$	\$
QALYs gained	0.8972	0.7584	0.1388
Incremental cost/extra QALY gained			\$ ²

Source: Table 3.5, p68 of the resubmission.

Abbreviations: FOLFIRINOX, fluorouracil, folinic acid, irinotecan, oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; ICER, Incremental cost-effectiveness ratio; LY, life-year; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; QALY, quality-adjusted life-year.

^a The comparator in the March 2024 submission consisted of Gem+NabP only.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$35,000 to < \$45,000

6.83 The resubmission presented an ICER of \$45,000 to < \$55,000/QALY gained. This represents an increase of almost \$15,000 to < \$25,000 /QALY gained compared to \$25,000 to < \$35,000 /QALY gained in the March 2024 submission base case.

6.84 The results of key univariate and multivariate sensitivity analyses are summarised in the table below.

Table 17: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER (\$/QALY gained)	% change to ICER
Base case	\$	0.1658	\$ ¹	
Time horizon (base case 5 years)				
3 years	\$	0.1491	\$ ¹	+ %
Discount rate (base case: 5%)				
0%	\$	0.1747	\$ ¹	- %
3.5%	\$	0.1683	\$ ¹	- %
OS switch from KM to extrapolation (base-case = 10% patients at-risk)				
GebSKI approach (ESC preferred)	\$	0.1850	\$ ¹	- %
Source of FOLFIRINOX OS and PFS curves (base-case = HR from MAIC of NALIRIFOX VS FOLFIRINOX)				
Assumed to be non-inferior to Gem+NabP	\$	0.1275	\$ ²	+ %
Assumed to be non-inferior to NALIRIFOX	\$	0.0956	\$ ³	+ %
Health state utility values (base case = EQ-5D-5L with UK weights from NAPOLI-3 trial [Free of Progression=0.85, Progressed=0.78])				
EQ-5D-5L with AU weights from NAPOLI-3 trial (Free of Progression=0.89, Progressed=0.82)	\$	0.1735	\$ ¹	- %
SEIGE trial- Devlin value set (Free of Progression=0.79, Progressed=0.75)	\$	0.1533	\$ ²	+ %
SEIGE trial- crosswalk method (Free of Progression=0.70, Progressed=0.65)	\$	0.1363	\$ ²	+ %
Romanus 2012- UK adjustment (Free of Progression=0.74, Progressed=0.67)	\$	0.1446	\$ ²	+ %
Adjusted proportions of mixed comparator (base case = 75% Gem+NabP/25% FOLFIRINOX)				
50% Gem+NabP/50% FOLFIRINOX	\$	0.2041	\$ ⁴	- %
0% Gem+ NabP/100% FOLFIRINOX	\$	0.2807	\$ ⁵	- %
NALIRIFOX assumed to be noninferior to FOLFIRINOX and adjusted proportions of mixed comparator				
75% Gem+NabP/25% FOLFIRINOX	\$	0.0956	\$ ³	+ %
50% Gem+NabP/50% FOLFIRINOX	\$	0.0637	\$ ⁶	+ %
25% Gem+NabP/75% FOLFIRINOX	\$	0.0319	\$ ⁷	+ %
0% Gem+ NabP/100% FOLFIRINOX	\$	0.0000	NA	NA

Source: Table 3.7, p72 of the resubmission, additional sensitivity analyses compiled during the evaluation.

Abbreviations: AU, Australian; ESC, Economics Sub Committee; EQ-5D-5L, EuroQol 5-dimension health status questionnaire (5 level); FOLFIRINOX, fluorouracil, folinic acid, irinotecan, oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect treatment comparison; NA, not applicable; NALIRIFOX, nanoliposomal irinotecan in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; UK, United Kingdom.

Note: Results in italics represent sensitivity analyses undertaken during the evaluation.

Note: The SEIGE trial was a Phase II, dose-scheduling trial of Gem+NabP with EQ-5D-5L data captured over a period of 12 months.

Romanus et al, 2012 was a health-related quality of life study of US patients with advanced pancreatic cancer deemed not appropriate for surgical resection. Utility values adjusted to the UK population were from NICE's assessment of Gem+NabP.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

⁴ \$35,000 to < \$45,000

⁵ \$25,000 to < \$35,000

⁶ \$135,000 to < \$155,000

⁷ \$255,000 to < \$355,000

6.85 The ICER was most sensitive to the comparative effectiveness of NALIRIFOX vs FOLFIRINOX (increased by % if assumed that NALIRIFOX is non-inferior to FOLFIRINOX), followed by the assumed proportions of the mixed comparator

(decreased by 1% if assume comparator is FOLFIRINOX only) and alternative sources of health state utility values (+1% when using utility values from the SEIGE trial [crosswalk method]).

- 6.86 If it is assumed NALIRIFOX is non-inferior to FOLFIRINOX, the ICER is extremely sensitive to the assumed proportions of the mixed comparator, driven by the incremental costs of NALIRIFOX compared to FOLFIRINOX (+\$1) (with 0 incremental QALYs generated if FOLFIRINOX is considered to be a sole comparator).
- 6.87 Regarding the comparison with Gem+NabP, the ESC considered that the observed benefit of NALIRIFOX demonstrated in NAPOLI-3 of ~1.9 months in terms of PFS and OS may not be clinically meaningful.
- 6.88 The Pre-PBAC Response maintained the approach taken in the submission was appropriate and stated the sponsor would not accept a cost minimisation approach based on FOLFIRINOX due to its limited use in treatment in patients with good performance status.

NALIRIFOX cost/patient/course

- 6.89 A summary of the drug cost per patient per course based on the proposed effective price for nal-IRI is presented in Table 18. The resubmission assumed a 40% rebate on NabP.

Table 18: Drug cost per patient per course for proposed and comparator drugs

	NALIRIFOX			Comparator (75% Gem+NabP/25% FOLFIRINOX)		
	Trial dose and duration (NAPOLI-3)	Model	Financial estimates	Trial dose and duration (NAPOLI-3 and ACCORD11/PRODIGE4)	Model	Financial estimates
Mean dose	nal-IRI: 50mg/m ² 5-FU: 2400 mg/m ² Oxaliplatin: 60 mg/m ² Folinic acid: 400mg/m ²	nal-IRI: 50mg/m ² 5-FU: 2400 mg/m ² Oxaliplatin: 60 mg/m ² Folinic acid: 50mg/m ²		Gem+NabP Gem:1000 mg/m ² NabP:125 mg/m ² FOLFIRINOX Irinotecan: 180 mg/m ² 5-FU: 2400 mg/m ² 5-FU (bolus): 400 mg/m ² Oxaliplatin: 85 mg/m ² Folinic acid: 400 mg/m ²	Gem+NabP Gem:1000 mg/m ² NabP:125 mg/m ² FOLFIRINOX Irinotecan: 180 mg/m ² 5-FU: 2400 mg/m ² 5-FU (bolus): 400 mg/m ² Oxaliplatin: 85 mg/m ² Folinic acid: 50 mg/m ²	
Mean number of treatment cycles	6.5			Gem+NabP: 5.1 FOLFIRINOX: 5.0	Gem+NabP: 5.1 FOLFIRINOX ^a : 6.3	
Cost/patient/cycle ^b	\$█	\$█		Gem+NabP: \$█ FOLFIRINOX: \$█	Gem+NabP: \$█ FOLFIRINOX: \$█	
Cost/patient/course ^c	\$█	\$█		Gem+NabP: \$█ FOLFIRINOX: \$█	Gem+NabP: \$█ FOLFIRINOX: \$█	

Source: Table 3.4, p66 of the resubmission.

Abbreviations: 5-FU, 5-fluorouracil; FOLFIRINOX, fluorouracil, folinic acid, irinotecan, oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; PFS, progression free survival.

^a The number of treatment cycles of FOLFIRINOX in the economic model and financial estimates was based on the median number of cycles reported in the GENERATE trial.

^b NALIRIFOX and FOLFIRINOX treatment regimens consist of 2x drug administrations/cycle, Gem+NabP treatment regimen consists of 3x drug administrations/cycle.

^c Cost per patient per course was calculated by multiplying the cost per patient per cycle (informed by patient level data from the NAPOLI-3 [NALIRIFOX and Gem+NabP] and ACCORD11/PRODIGE4 [FOLFIRINOX] trials) by the mean number of treatment cycles for NALIRIFOX and Gem+NabP (from NAPOLI-3) and the median number of treatment cycles for FOLFIRINOX (from GENERATE).

Note: Costs of Gem+NabP include an assumed 40% rebate applied to the costs of NabP

6.90 Other than the changed rebates applied to the costs of nal-IRI and NabP, the resubmission used a 50 mg flat dose of folinic acid in the economic model and financial estimates for the NALIRIFOX and FOLFIRINOX regimens, rather than BSA-based dosing at 400 mg/m² as was administered in the clinical trials. This dosage reflects advice that the eviQ guidelines will be updated to recommend 50 mg flat dosing of folinic acid for these regimens.

Estimated PBS usage & financial implications

6.91 This submission was not considered by DUSC.

6.92 The resubmission used an epidemiological approach to estimate the PBS usage and financial implications associated with the proposed listing of nal-IRI.

6.93 A summary of the key inputs in the financial analysis is presented in Table 19.

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Table 19: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population		
Incident patients – pancreatic cancer	4,930 in year 1, increasing to 5,818 in Year 6 AIHW Projected Incidence of pancreatic cancer: People (2025-2030)	Updated data have been utilised in the resubmission. This is appropriate.
Proportion of incident patients with mPAC	80% Malik 2012; Puckett 2022; Santucci 2022; Cancer Council 2022; AJGP 2019.	This estimate includes patients with both Stage III (locally advanced/unresectable) and Stage IV (metastatic) pancreatic cancer. The ESC previously considered that most patients with Stage III disease would progress to Stage IV disease and determined that the estimated value was reasonable (para 6.100, irinotecan (nanoliposomal), PSD, March 2024 PBAC submission).
Proportion of mPAC patients receiving systemic therapy	57.30% Santucci 2022, PURPLE registry.	This is reasonable
Proportion of mPAC patients receiving systemic therapy with ECOG PS 0 or 1	92.30% PURPLE registry	This is reasonable.
Treatment utilisation		
Current market share of treatments for eligible population in Australia	85.1% Gem+NabP/14.9% FOLFIRINOX PURPLE registry	From the analysis of the PURPLE registry by Lee 2023, the market share of first-line treatments for patients with locally advanced, recurrent or metastatic pancreatic cancer was 66.5% Gem+NabP, 10.9% FOLFIRINOX and 23% other therapies. As such, the proposed proportions may overestimate the current market share of Gem+NabP and FOLFIRINOX within the eligible population. The financial estimates are sensitive to this input.
Extent of substitution of Gem+NabP and FOLFIRINOX by NALIRIFOX	Gem+NabP: █████% in Year 1, █████% in Year 2 onwards FOLFIRINOX: 75% in Year 1, █████% from Year 2 onwards Assumption	This is a change from the March 2024 submission, which assumed substitution of Gem+NabP by NALIRIFOX of up to █████% and assumed no substitution of FOLFIRINOX. The extent to which NALIRIFOX will substitute for Gem+NabP in clinical practice is uncertain given the toxicity profile for NALIRIFOX. The financial estimates are sensitive to this input.
Uptake rate of NALIRIFOX	█████% Year 1, █████% Years 2-6 Calculated by sum of current market share and assumed extent of substitution of Gem+NabP and FOLFIRINOX	Likely overestimated given that the market share of Gem+NabP and FOLFIRINOX was overestimated and the extent to which Gem+NabP and FOLFIRINOX will be substituted by NALIRIFOX is uncertain.
Number treated	█████ ¹ in Year 1, increasing to █████ ¹ in Year 6 Calculated from number of eligible patients x uptake rate	Likely overestimated, given the uptake rate is overestimated.
Average duration of treatment per patient	6.5 cycles (2 administrations per cycle) NAPOLI-3 trial	This is consistent with the treatment duration applied in the economic evaluation.

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Parameter	Value applied and source	Comment
Scripts dispensed	█ ² in Year 1, increasing to █ ² in Year 6 Number treated x 13 (average scripts per patient [2 administrations per cycle x 6.5 cycles])	Calculation of scripts dispensed has been verified.
Costs		
Nal-IRI	\$1300 – Published AEMP	A █% Special Pricing Arrangement rebate is applied (increased from █% in the March 2024 submission)
Affected medications	Includes components of NALIRIFOX (oxaliplatin, 5-FU, Leucovorin), Gem+NabP and FOLFIRINOX	Costs of substituted Gem+NabP is based on recommended dosing and mean number of treatment cycles from NAPOLI-3 trial and applies an assumed 40% rebate on government expenditure of NabP. Costs of substituted FOLFIRINOX is based on recommended dosing from ACCORD11/PRODIGE4 trial but uses the median number of treatment cycles from the GENERATE trial. Financial estimates were not sensitive to the number of treatment cycles of FOLFIRINOX used.
MBS costs	\$118.30 MBS item number 13950	This is appropriate. Net costs to MBS decreased in comparison with the previous submission as a result of substitution of Gem+NabP (3 administrations per cycle) by NALIRIFOX (2 administrations per cycle).

Source: Compiled during the evaluation

Abbreviations: AEMP, Approved ex-manufacturer price; AIHW, Australian Institute of Health and Welfare; FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; MBS, Medicare Benefits Schedule; mPAC, metastatic pancreatic adenocarcinoma; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; PBS, Pharmaceutical Benefits Scheme; PURPLE, Pancreatic cancer: Understanding Routine Practice & Lifting End registry; RPBS, Repatriation Pharmaceutical Benefits Scheme.

Blue shading indicates these data sources and key inputs were unchanged from the original submission

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

6.94 The estimated use and financial implications of PBS listing of nal-IRI is presented in Table 20. These results are based on an assumed 40% rebate on NabP.

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Table 20: Estimated use and financial implications

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)	Total over 6 years
Estimated extent of use							
Number of patients treated	1	1	1	1	1	1	2
Number of scripts dispensed ^a	3	3	3	3	3	3	4
Estimated financial implications of nal-IRI							
Cost to PBS/RPBS less copayments	\$5	\$5	\$5	\$5	\$6	\$6	\$10
Estimated financial implications for other medicines^b							
Cost to PBS/RPBS less copayments	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Net financial implications							
Net cost to PBS/RPBS	\$8	\$5	\$5	\$5	\$5	\$5	\$9
Net cost to MBS	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Net cost to Australian Government health budget	\$8	\$5	\$5	\$5	\$5	\$5	\$9
Previous submission (March 2024 PBAC meeting)							
Net cost to PBS/RPBS	\$5	\$5	\$5	\$5	\$5	\$5	\$11
Net cost to MBS (80%)	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Net cost to Australian Government health budget	\$5	\$5	\$5	\$5	\$5	\$5	\$11

Source: Compiled and corrected during the evaluation

Abbreviations: MBS, Medicare Benefits Schedule; nal-IRI, nanoliposomal irinotecan; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

^a Assuming 13 scripts per patient per treatment course as estimated by the resubmission.

^b Assumed split of substituted market share of Gem+NabP(75%) and FOLFIRINOX(25%)

Note: Results in italics represent corrected values.

Blue shading indicates these data sources and key inputs were unchanged from the original submission

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 90,000 to < 100,000

⁵ \$10 million to < \$20 million

⁶ \$20 million to < \$30 million

⁷ net cost saving

⁸ \$0 to < \$10 million

⁹ \$60 million to < \$70 million

¹⁰ \$100 million to < \$200 million

¹¹ \$90 million to < \$100 million

6.95 The net cost to the Australian Government health budget of listing nal-IRI was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing. This compares to a total of \$90 million to < \$100 million in the first 6 years of listing in the March 2024 submission.

6.96 The financial estimates were likely overestimated. This was due to the market share of Gem+NabP and FOLFIRINOX being overestimated (as up to 23% of PAC patients may receive other first-line chemotherapy options) and uncertainty around the extent to which Gem+NabP may be substituted by NALIRIFOX in clinical practice.

6.97 Results of key sensitivity analyses undertaken during the evaluation are presented in Table 21.

Table 21: Results of sensitivity analyses for financial estimates conducted during the evaluation

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)	Total over 6 years	% change
Net cost health system (base case)	\$█ ¹	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ³	-
Extent of substitution of Gem+NabP by NALIRIFOX (base case: █% in Year 1, █% in Years 2-6)								
Assume constant at 25% across all years	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	-37%
Assume substitution of FOLFIRINOX only (0% Gem+NabP)	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ²	-76%
Market share of Gem+NabP and FOLFIRINOX (base case=85.1% Gem+NabP/14.9% FOLFIRINOX)								
66.5% Gem+NabP/ 10.9% FOLFIRINOX	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ⁴	-24%

Source: Compiled during the evaluation.

Abbreviations: Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin.

Note: Results in italics represent sensitivity analyses undertaken during the evaluation.

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

³ \$60 million to < \$70 million

⁴ \$40 million to < \$50 million

6.98 The financial estimates are highly sensitive to the assumed extent of substitution of Gem+NabP by NALIRIFOX and the estimated market share of Gem+NabP and FOLFIRINOX (collectively forming the proposed uptake rate of NALIRIFOX). The PBAC previously noted that financial estimates were highly sensitive to the medicines replaced (para 7.14, irinotecan (nanoliposomal), PSD, March 2024 PBAC submission).

6.99 The ESC advised that given its view the comparator and therapy most likely to be replaced in practice would be FOLFIRINOX (rather than Gem+NabP) and that the utilisation and financial estimates should be revised on that basis.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of nanoliposomal irinotecan (nal-IRI), as part of the NALIRIFOX regimen (containing oxaliplatin, 5-fluorouracil (5-FU) and folinic acid/leucovorin), for the treatment of metastatic pancreatic adenocarcinoma (mPAC). Consistent with its previous advice, the PBAC considered that the combination regimen known as FOLFIRINOX (containing irinotecan, 5-FU, LV and oxaliplatin) was the relevant main comparator in the proposed population, rather than gemcitabine with nanoparticle albumin-bound paclitaxel (Gem+NabP) as nominated by the resubmission. In not recommending the listing, the Committee considered the resubmission had not substantively addressed its previous concerns relating to the comparator and that the comparative clinical evidence did not adequately support the

claims made in the submission. Therefore, the PBAC considered the economic analysis approach taken by the resubmission was not informative.

- 7.2 The main reason for this outcome was due to inappropriate comparator selection.
- 7.3 The PBAC recognised there remains a high clinical need for effective therapies for mPAC and there is a strong desire from patients and their families for improved treatments. However, the Committee considered the presented evidence did not adequately support a conclusion that the NALIRIFOX regimen is superior in terms of comparative effectiveness or safety to the FOLFIRINOX regimen (containing regular irinotecan), therefore a listing of nal-IRI would not substantively address this need.
- 7.4 The Committee noted the resubmission had amended the requested listing to exclude patients with an ECOG performance status of 2, aligning the requested population for nal-IRI (as part of the NALIRIFOX regimen) with that of standard irinotecan (as part of the FOLFIRINOX regimen) and considered this was reasonable, as the populations and place in therapy for these treatments were effectively the same.
- 7.5 The PBAC recalled the original submission in March 2024 had nominated a chemotherapy regimen of gemcitabine plus nanoparticle albumin-bound paclitaxel (Gem+NabP) as the sole comparator and its advice that any resubmission should nominate FOLFIRINOX as the main comparator, and if there was insufficient evidence to support a claim of superiority of the NALIRIFOX over FOLFIRINOX, the appropriate form of economic evaluation would be a cost minimisation approach (see paragraph 5.3-5.5). The Committee noted the resubmission had nominated a weighted comparator of 75% Gem+NabP and 25% FOLFIRINOX, with the PSCR arguing that NALIRIFOX will primarily replace Gem+NabP in practice and that a cost minimisation would result in a lower price for NALIRIFOX than Gem+NabP, which the sponsor considered was inappropriate as there was randomised controlled trial (RCT) evidence showing superior overall survival (OS) for NALIRIFOX over Gem+NabP (see paragraph 5.6). However, the PBAC considered that in practice, the population most likely to be considered for NALIRIFOX was most aligned with the population who would receive FOLFIRINOX and considered the nomination of Gem+NabP as the primary comparator remained inappropriate. The PBAC considered this view on the likely population and appropriate comparator for NALIRIFOX was further reinforced by the available safety data, which indicated the adverse event profiles of NALIRIFOX and Gem+NabP are different, and the gastrointestinal side effects of NALIRIFOX are more likely to require hospitalisation and negatively impact quality of life, whilst NALIRIFOX and FOLFIRINOX are likely to have similar toxicities (discussed further below). Furthermore, as the Committee considered the evidence did not substantiate a claim that NALIRIFOX is superior to FOLFIRINOX (discussed further in the paragraphs below), and the resubmission did not identify a cohort of patients who could not receive FOLFIRINOX but could be considered eligible for NALIRIFOX, that the weighted comparator approach used in the submission was also inappropriate. On that basis, the PBAC reaffirmed its previously expressed view that FOLFIRINOX was the appropriate comparator for NALIRIFOX.

- 7.6 The PBAC noted that compared to the March 2024 submission, the resubmission had not included any new clinical trials but noted updated results for the overall survival (OS) outcome from the pivotal NAPOLI-3 trial out to a median follow-up of 29.5 months was provided (based on patient-level data and a poster presentation, see paragraph 6.7). The PBAC also noted the presented evidence from the GENERATE trial, which was used to inform a single-step indirect treatment comparison (ITC) of NALIRIFOX and FOLFIRINOX, remained limited to an abstract, a deck of presentation slides and a published protocol (see paragraph 6.6). The Committee further noted that whilst the MPACT and ACCORD11/PRODIGE4 trials from the previous submission were included, the resubmission argued the multi-step indirect treatment comparisons (ITCs) of NALIRIFOX and FOLFIRINOX (via comparators Gem+NabP in MPACT and gemcitabine monotherapy in MPACT and ACCORD11/PRODIGE4) should be considered less reliable than the single-step ITC based on the GENERATE trial.
- 7.7 The PBAC considered that, in principle, a single-step ITC may typically be preferred to a multi-step ITC, as steps through additional comparators add inherent additional uncertainty to any such comparisons; however, the PBAC also considered that the robustness of the trials, their exchangeability, transitivity issues and applicability to the Australian context are important factors when considering whether a comparison is reliable and informative to support decision-making. The PBAC considered that based on the limited available information, the GENERATE trial was not a reliable basis for assessing the comparative effectiveness of NALIRIFOX and FOLFIRINOX, because compared to the pivotal NAPOLI-3 trial, GENERATE had a different population and setting (GENERATE was limited to Japan and people of Asian heritage), used a modified FOLFIRINOX regimen (mFOLFIRINOX), patients tended to be older and had generally better baseline performance status, as well as different proportions with liver metastases and 2 or more metastatic sites (lower in GENERATE) (discussed further in paragraph 6.15). Furthermore, the PBAC also reiterated previous concerns that the results of the GENERATE trial, which reported a median OS of 17.0 months with Gem+NabP, appeared to be incongruent with the 9.2 months median OS reported in NAPOLI-3, and inconsistent with the results of the multi-step ITC and published analysis (Nichetti 2024) it had considered in March 2024.
- 7.8 Overall, the PBAC considered the NAPOLI-3 and GENERATE trials were likely not sufficiently exchangeable for an ITC to be reliable, and considered the matching-adjusted indirect comparison (MAIC) approach, which used a propensity score model to re-weight individual patient-level data from NAPOLI-3 onto GENERATE, had not or could not account for multiple variables which may be impactful (see paragraph 6.35), and the lack of available detail about the GENERATE trial led to substantial uncertainty about whether a MAIC analysis could overcome the numerous differences between the trials. The PBAC considered the issues with the GENERATE trial remained too substantial for it to be considered reliable to assess the comparative effectiveness of NALIRIFOX and FOLFIRINOX, and therefore reaffirmed its view expressed in March 2024 that a claim of superior comparative effectiveness of NALIRIFOX over

FOLFIRINOX was not supported.

- 7.9 In terms of comparative safety compared to FOLFIRINOX, the Committee considered the results of the presented ITC to be unreliable given the concerns about the GENERATE study (discussed above), and recalled the available data it had previously considered, including the Nichetti 2024 study, suggested that NALIRIFOX and FOLFIRINOX have similar toxicities. Therefore, the PBAC considered the claim that NALIRIFOX has advantages over FOLFIRINOX in terms of comparative safety was not adequately supported.
- 7.10 The PBAC noted the resubmission presented a cost utility analysis based on a weighted comparator approach, nominating a weighting of 75% Gem+NabP and 25% FOLFIRINOX. The Committee recalled it had previously stated that any resubmission would need to nominate FOLFIRINOX as the main comparator, and if there was insufficient evidence to support a claim of superior comparative effectiveness or safety, the appropriate form of economic evaluation would be a cost minimisation approach (see paragraph 5.5). Noting the resubmission had neither nominated FOLFIRINOX as the main comparator, nor adequately supported claims of superior comparative effectiveness or safety, nor adequately justified that the population who would likely be considered eligible for NALIRIFOX was different to FOLFIRINOX, the PBAC considered the economic evaluation approach taken by the submission to be inappropriate and reaffirmed its previously expressed view with respect to the appropriate form of economic evaluation.
- 7.11 The PBAC noted the resubmission estimated NALIRIFOX would replace approximately 1% of Gem+NabP use (see Table 19) and considered this was likely to be overestimated, given its view that the NALIRIFOX was more likely to be used in the population who would be considered for FOLFIRINOX. Therefore, the Committee considered the utilisation and financial estimates likely overestimated the use of NALIRIFOX in practice, as it would predominantly replace FOLFIRINOX.
- 7.12 The PBAC considered any re-submission should be a standard re-entry submission and noted it may be lodged at any future standard due date for PBAC submissions using this pathway.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the

merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Servier is disappointed by this outcome. Servier thanks the clinical community who had provided advice to inform the two submissions to PBAC, and thanks the patient community for their valuable input to the PBAC. Servier reaffirms its commitment to people living with metastatic pancreatic cancer and will continue to make nal-IRI available for patients via a private script.