

**5.09 IRINOTECAN,
43 mg irinotecan (nanoliposomal) in 10 mL injection,
Onivyde[®],
Baxalta Australia Pty Ltd.**

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for irinotecan (in the form of I.V. injection containing nanoliposomal irinotecan 43 mg in 10 mL, hereafter referred to as irinotecan (nanoliposomal)), in combination with 5-fluorouracil (5-FU) and folinic acid for the treatment of metastatic pancreatic adenocarcinoma in adult patients with disease progression who have previously received gemcitabine-based therapy.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	DPMQ (published)	DPMQ (effective)	Proprietary Manufacturer	Name and
IRINOTECAN irinotecan - nanoliposomal 43 mg/10 mL injection, 10 mL vial	160 mg	11	\$ [REDACTED] (public) \$ [REDACTED] (private)	\$ [REDACTED] (public) \$ [REDACTED] (private)	Onivyde	Baxalta (now part of Shire Australia)

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
PBS Indication:	Stage IV (metastatic) adenocarcinoma of the pancreas
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Treatment phase:	Initial treatment
Clinical criteria:	The treatment must be in combination with 5-fluorouracil and folinic acid; AND <i>The condition</i> must have progressed <i>following</i> treatment with gemcitabine based therapy; AND Patient must not have previously received PBS-subsidised treatment with nanoliposomal irinotecan for this indication <i>this drug for this condition.</i>
Administrative Advice	<i>Special Pricing Arrangements apply.</i>

Treatment phase:	Continuing treatment
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Clinical criteria:	<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND The treatment must be in combination with 5-fluorouracil and folinic acid; AND Patient must have stable or responding disease.</i>
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- 2.2 Listing was requested on a cost-effectiveness basis compared with 5-FU/folinic acid and the mFOLFOX6 regimen (oxaliplatin plus 5-FU/folinic acid).

3 Background

- 3.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation, irinotecan (nanoliposomal) was being considered by the TGA delegate for the treatment of metastatic pancreatic adenocarcinoma, in combination with 5-FU/folinic acid in adult patients who have previously received gemcitabine-based therapy. The first round TGA clinical evaluation report and draft product information (PI) for irinotecan (nanoliposomal) were available during the evaluation.
- 3.2 The TGA Delegate's Summary and the ACPM resolution were received prior to the PBAC meeting. The ACPM resolved to recommend to the TGA Delegate that irinotecan (nanoliposomal) to have an overall positive benefit-risk profile for the proposed indication: the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU/folinic acid in adult patients who have been previously treated with gemcitabine-based therapy.
- 3.3 The proposed PI states that the dose and regimen for irinotecan (nanoliposomal) in combination with 5-FU/folinic acid is as follows: 70 mg/m² irinotecan (nanoliposomal) intravenously over 90 minutes, followed by 400 mg/m² folinic acid intravenously over 30 minutes, followed by 2,400 mg/m² 5-FU intravenously over 46 hours, administered every 2 weeks.
- 3.4 The PBAC had not previously considered irinotecan (nanoliposomal).
- 3.5 Any further reference to irinotecan (nanoliposomal) refers to its use in combination with 5-FU/folinic acid.

4 Clinical place for the proposed therapy

- 4.1 The most common and aggressive type of pancreatic cancer is adenocarcinoma, which is usually asymptomatic in early stages and diagnosed at the locally advanced or metastatic stages. There are significant co-morbidities (e.g. pain, jaundice, weight loss) and mortality associated with the disease. The ESC noted that prognosis is poor with low five-year survival rates and that new, more effective, treatments for this condition are required.
- 4.2 The ESC noted that irinotecan (nanoliposomal) is a novel form of irinotecan, which is encapsulated in a lipid membrane. The liposomal formulation is intended to prevent

the water-soluble irinotecan from converting to its more active metabolite, SN-38, prior to reaching the tumour.

- 4.3 The submission positioned irinotecan (nanoliposomal) as an alternative treatment in patients with metastatic pancreatic adenocarcinoma who have disease progression after previous treatment with gemcitabine-based therapy in any setting or line of therapy (e.g. first-line, second-line, third-line, adjuvant, neo-adjuvant or post-surgical). The combination of paclitaxel nanoparticle albumin bound (Abraxane[®]) and gemcitabine is currently available through the PBS for first-line treatment of metastatic pancreatic adenocarcinoma. An irinotecan-containing regimen, FOLFIRINOX (a combination of the chemotherapy drugs fluorouracil [5-FU], leucovorin, irinotecan and oxaliplatin), is an alternative first-line treatment that is being used by some clinicians.
- 4.4 The algorithm presented in the submission was a simplified representation of the complex patient flow and multiple treatment options available. The algorithm was consistent with the proposed PBS restriction but it was unclear if the choice of treatment would flow strictly according to lines of therapy. In clinical practice, treatment choice would likely be influenced by other factors such as previous therapy, disease severity, patient performance status and risk of adverse events.
- 4.5 Treatment options in the algorithm presented in the submission were consistent with published guidelines for metastatic pancreatic cancer, generally recommending fluoropyrimidine-based therapy for patients who previously received gemcitabine-based therapy. Recommended treatment options that were fluoropyrimidine-based included irinotecan-containing regimens (e.g. FOLFIRI, FOLFIRINOX) and oxaliplatin-containing regimens (e.g. XELOX, mFOLFOX6 or OFF). None of the guidelines mentioned the use of 5-FU/folinic acid alone or capecitabine as monotherapy.

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

5 Comparator

- 5.1 5-FU/folinic acid was nominated as a primary comparator based on availability of data and its use as a control in clinical trials. The evaluation considered this was not appropriate justification for a comparator. The PSCR argued that expert opinion affirmed that 5-FU/folinic acid is representative of the range of therapies (including fluoropyrimidine-based comparators such as capecitabine) that are used in the proposed target patient population, due to its status as a pro drug which is metabolised to 5-FU. The ESC considered there was limited data presented in the submission to justify that 5-FU/folinic acid could be a reasonable proxy. Given that utilisation data provided by the sponsor indicated that 5-FU/folinic acid alone is not widely used in practice the ESC considered that it was not an appropriate comparator.
- 5.2 The submission also nominated the mFOLFOX6 (5-FU/folinic acid plus oxaliplatin) regimen as a primary comparator as it is one of the most commonly used treatments in patients failing gemcitabine-based therapy. Market research provided in the submission supported this claim, although the data and published guidelines also

suggested a wide range of other treatment options such as capecitabine monotherapy, XELOX (capecitabine plus oxaliplatin), FOLFIRI (5-FU/folinic acid plus irinotecan), FOLFIRINOX (5-FU/folinic acid plus irinotecan plus oxaliplatin), or OFF (5-FU/folinic acid plus oxaliplatin, which may be superseded by the mFOLFOX6 the dosing regimen) are also used.

- 5.3 Given the wide range of treatment regimens available to patients previously treated with gemcitabine-based therapy, the ESC considered that the submission inadequately justified the choice of comparators. The PSCR (p1) argued that ‘the comparators presented in the submission are representative of current treatment practice based on expert advice, up-to-date and well-regarded Australian treatment guidelines, and published trials [in metastatic pancreatic adenocarcinoma]’. The ESC considered that oxaliplatin-containing combination regimens, such as mFOLFOX6, were appropriate comparators.
- 5.4 The PSCR further stated that ‘FOLFIRI is less frequently used in pancreatic cancer and it is not indicated for use in metastatic pancreatic cancer’ and that ‘FOLFIRINOX is not considered a comparator as it is used primarily in a first line setting and for patients with good performance status’. The ESC agreed that FOLFIRI is not commonly used and that FOLFIRINOX is increasingly being used in first-line (in addition to second-line use following failure with gemcitabine-based therapy). The ESC noted there is no evidence for efficacy for irinotecan (nanoliposomal) with 5-FU/folinic acid as second-line treatment following failure with the irinotecan containing FOLFIRINOX therapy.
- 5.5 The pre-PBAC response (p1) accepted that treatment with 5-FU/folinic alone is used infrequently for metastatic pancreatic adenocarcinoma. However, the pre-PBAC response argued that 5-FU/folinic acid is an appropriate comparator in the ‘historical context of the study’ and ‘has been accepted as relevant by registration authorities’.

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 presented clinical case studies, including current clinical treatments for patients with this condition, how the drug would be used in current practice in Australia, and addressed other matters in response to the Committee’s questions. The PBAC noted the information provided by the clinical expert at the sponsor hearing and considered that the hearing was informative as it provided a clinical perspective on the need for effective, non-toxic therapies for metastatic pancreatic adenocarcinoma. The clinician provided the PBAC with additional context of the clinical significance of the incremental benefit likely to be associated with irinotecan (nanoliposomal) and indicated that the toxicity is likely to be similar to other irinotecan-containing regimens. The clinician stated that mFOLFOX6 is an appropriate comparator and confirmed that 5-FU/folinic acid is not currently a commonly used treatment for this condition in Australia.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (1) and organisations (3 – Medical Oncology Group of Australia (MOGA), Pancare Foundation and Rare Cancers Australia) via the Consumer Comments facility on the PBS website. The comments described the potential benefit in overall survival associated with treatment with irinotecan (nanoliposomal) and the clinical need for an effective treatment for patients with second-line metastatic pancreatic adenocarcinoma.
- 6.3 The PBAC particularly noted that MOGA provided its support to the submission for irinotecan (nanoliposomal) and noted that its ESMO-MCBS evaluation score for non-curative therapies is 2 out of a maximum of 5 (where 5 and 4 represent the grades with substantial improvement)¹.

Clinical trials

- 6.4 The submission was based on one head-to-head trial comparing irinotecan (nanoliposomal) with 5-FU/folinic acid for the treatment of metastatic pancreatic cancer in patients with disease progression who have previously received gemcitabine-based therapy (NAPOLI-1).
- 6.5 The submission also presented a naïve indirect comparison of irinotecan (nanoliposomal) (NAPOLI-1) with oxaliplatin-containing regimens (CONKO-003 and PANCREOX).
- 6.6 Details of the trials presented in the submission are provided in Table 1.

¹ Cherny NI, Sullivan R, Dafni U, et al: 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* 26:1547-73, 2015

Table 1: Trials and associated reports included in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Irinotecan (nanoliposomal) plus 5-FU/folinic acid versus 5-FU/folinic acid		
NAPOLI-1 (NCT01494506)	Wang-Gillam A, Von Hoff DD, Li C-P, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial.	Lancet 387(10018):545-57, 6 Feb 2016
	Clinical study report: MM-398-07-03-01 (NAPOLI-1) (2015): A randomised, open-label phase 3 study of MM-398, with or without 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy.	Internal study report
	█ day safety update report of the NAPOLI-1 study. The report contains █ months of additional safety data from the NAPOLI-1 study, following the primary analysis cut-off date for the data presented from the NAPOLI-1 study which was █.	Internal study report
Meta-analysis comparing studies with oxaliplatin-containing regimens (OFF and mFOLFOX6) versus 5-FU/folinic acid		
CONKO-003 (NCT00786058)	Oettle et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial.	Journal of Clinical Oncology 32(23):2423-9, 10 Aug 2014
	Pelzer U et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase-III study from the German CONKO-study group.	European Journal of Cancer 47(11):1676-81, Jul 2011
PANCREOX (NCT01121848)	Gill S et al. PANCREOX: A randomised phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy [abstract].	Journal of Clinical Oncology, 2014 ASCO Annual Meeting Abstracts, 32(15_suppl):4022 [abstract only]

Source: Tables B.2.3 (p87) and B.6.14 (p139) of the submission

6.7 The key features of the included studies are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Irinotecan (nanoliposomal) vs. 5-FU/folinic acid						
NAPOLI-1	236	MC, R, OL 108 weeks + safety extension	High	Metastatic pancreatic cancer with disease progression failing gemcitabine-based therapy	OS, PFS	Extrapolated survival gain
Meta-analysis of oxaliplatin-containing regimens (OFF and mFOLFOX6) versus 5-FU/folinic acid						
CONKO-003	168	MC, R, OL (max follow-up 402 weeks)	High	Locally advanced or metastatic pancreatic cancer with disease progression after failing gemcitabine-based therapy	OS, PFS	No
PANCREOX	108	MC, R, OL (trial terminated early)	High	Advanced or metastatic pancreatic cancer with disease progression after failing gemcitabine-based therapy	PFS, OS	No
Meta-analysis	276	Included CONKO-003 and PANCREOX trials, comparison of OS and PFS				No

Source: compiled during the evaluation

Abbreviations: MC, multi-centre; OL, open-label; OS, overall survival; PFS, progression-free survival; R, randomised

- 6.8 All included trials had a high risk of bias. NAPOLI-1, CONKO-003 and PANCREOX were open-label trials. It was unclear if outcome assessors were blinded in the CONKO-003 and PANCREOX trials due to limited documentation in the publications. In the NAPOLI-1 trial, there was added potential for differential disease management and detection bias due to differences in frequency of monitoring between treatment arms.
- 6.9 The PANCREOX trial was terminated early due to insufficient accrual of patients. There was insufficient documentation available to adequately assess the robustness of the trial.
- 6.10 There were issues of applicability, and heterogeneity across the CONKO-003 and PANCREOX trials. The ESC noted that the CONKO-003 and PANCREOX trials included patients with earlier stage pancreatic cancer who were likely to have better survival than the target population. The trials were not comparable as the treatment arms of OFF, mFOLFOX6 and the comparator arms of 5-FU/folinic acid had different dosing regimens. The submission inappropriately assumed the OFF and mFOLFOX6 regimens to be equivalent. The PSCR (p3) noted that ‘the control arm is seen to perform better in NAPOLI-1 than in CONKO-003 with respect to overall survival’ despite these issues.
- 6.11 The ESC noted concerns with exchangeability between the NAPOLI-1 trial and the CONKO-003 and PANCREOX trials that would significantly limit the reliability of an indirect comparison given the differences between patient populations (e.g. baseline risk, prior lines of therapy) and dosing regimens (dose strength, frequency and cycles of administration). The ESC also considered that the PANCREOX trial had insufficient data for a thorough analysis to demonstrate better efficacy of irinotecan (nanoliposomal).

- 6.12 The PSCR and the pre-PBAC response argued that the usefulness of the naïve indirect meta-analysis evidence for the clinical benefit for irinotecan should be viewed in context of an uncommon disease with a very poor prognosis and limited treatment options.

Comparative effectiveness

- 6.13 Direct comparison with 5-FU/folinic acid: The main outcomes presented in the submission were from the NAPOLI-1 post-hoc analyses. The analyses were conducted using an additional [redacted] months follow-up from the primary analyses cut-off date (based on the later [redacted] cut-off date).
- 6.14 Overall survival (primary outcome) for irinotecan (nanoliposomal) compared with 5-FU/folinic acid is summarised in Table 3.

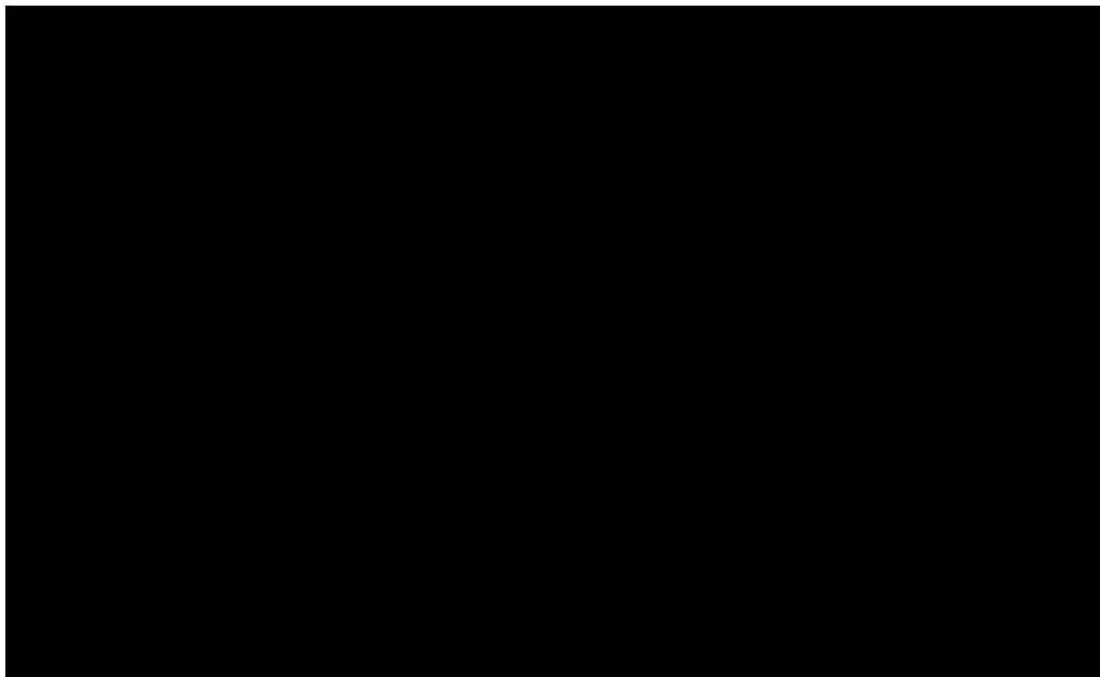
Table 3: Post-hoc analysis for overall survival (NAPOLI-1 trial)

Overall survival	Irinotecan (nanoliposomal) (N=117)	5-FU/folinic acid (N=119)	HR (95%CI)
Patients with events, n/N (%)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Median, weeks (95% CI)	[redacted] ([redacted])	[redacted] ([redacted])	p=[redacted]

Source: Table 14.2.1.1, Appendix 13 of the submission
 Abbreviations: CI, confidence interval; HR, hazard ratio

- 6.15 Treatment with irinotecan (nanoliposomal) was associated with a statistically significant increase of [redacted] weeks in median overall survival compared with 5-FU/folinic acid (HR [redacted], 95% CI: [redacted], [redacted]). Figure 1 summarises the updated results for overall survival from NAPOLI-1 with the safety extension data.

Figure 1: Updated Kaplan-Meier curves for overall survival (ITT population) using NAPOLI-1 safety extension data



Source: Figure B.6.1, p115 of the submission

Abbreviations: CI, confidence interval; LV, folinic acid; MM-398, irinotecan (nanoliposomal)

- 6.16 The results from the post-hoc analysis (see Table 3) were consistent with the primary analysis which favoured irinotecan (nanoliposomal) compared with 5-FU/folinic acid (primary analysis: HR 0.67 (95% CI: 0.49, 0.92)).
- 6.17 Progression-free survival for irinotecan (nanoliposomal) compared with 5-FU/folinic acid is summarised in Table 4.

Table 4: Post-hoc analysis for progression-free survival (NAPOLI-1 trial)

Progression-free survival	Irinotecan (nanoliposomal) (N=117)	5-FU/folinic acid (N=119)	HR (95%CI)
Patients with event, n/N (%)	██████████ (██████████)	██████████ (██████████)	██████████ (██████████, ██████████) p=██████████
Progressed, n/N (%)	██████████ (██████████)	██████████ (██████████)	
Died, n/N (%)	██████████ (██████████)	██████████ (██████████)	
Median, weeks (95%CI)	██████████ (██████████, ██████████)	██████████ (██████████, ██████████)	

Source: Table 14.2.2.1, Appendix 13 of the submission

Abbreviations: CI, confidence interval; HR, hazard ratio

- 6.18 Treatment with irinotecan (nanoliposomal) was associated with a statistically significant increase in median progression-free survival of ██████████ weeks compared with 5-FU/folinic acid (HR ██████████, 95% CI: ██████████, ██████████).
- 6.19 Results from the post-hoc analysis were consistent with the primary analysis, favouring irinotecan (nanoliposomal) compared with 5-FU/folinic acid (primary analysis: HR ██████████ 95% CI ██████████, ██████████) with the majority of events being progression but the difference in treatment effect significantly driven by mortality.

- 6.20 The ESC considered that the comparison of irinotecan (nanoliposomal) and 5-FU/folinic acid was uninformative if 5-FU/folinic acid is not a relevant comparator.
- 6.21 Indirect comparison with oxaliplatin-containing regimens: A naïve indirect comparison of overall survival and progression-free survival in the NAPOLI-1, PANCREOX and CONKO-003 trials is summarised in Table 5.

Table 5: Overall survival and progression-free survival (NAPOLI-1, PANCREOX and CONKO-003 trials)

Trial	Treatment	Comparator ^a	Overall survival HR (95%CI)	Progression-free survival HR (95%CI)
Meta-analysis of PANCREOX and CONKO-003 trials				
PANCREOX (N=108)	mFOLFOX6 (N=54)	5-FU/folinic acid (N=54)	1.78 (1.08, 2.93)	1 (0.66, 1.53)
CONKO-003 (N=160)	OFF (N=76)	5-FU/folinic acid (N=84)	0.66 (0.48, 0.91)	0.68 (0.50, 0.94)
Pooled (random effects)			1.06 (0.40, 2.81)	0.80 (0.55, 1.17)
NAPOLI-1 trial (post-hoc analysis)				
NAPOLI-1 (N=236)	Irinotecan (nanoliposomal) (N=117)	5-FU/folinic acid (N=119)	■ (■, ■)	■ (■, ■)

Source: Table B.6.23, p155 of the submission

Abbreviations: CI, confidence interval; HR, hazard ratio; mFOLFOX6, oxaliplatin plus 5-FU/folinic acid (2 week-cycle); OFF, oxaliplatin plus 5-FU/folinic acid (6-week cycle)

^aComparator treatments were administered using different dose strengths, frequencies and cycle lengths

- 6.22 For the pooled results from the CONKO-003 and PANCREOX trials the difference across the treatment arms for overall survival and progression-free survival were not statistically significant.
- 6.23 The meta-analysed results were of limited reliability given the significant issues of heterogeneity and comparability (mFOLFOX6, OFF and 5-FU/folinic acid arms had different dose strengths and cycles of administration; contrasting results from individual trials suggesting that OFF was superior to 5-FU/folinic acid but mFOLFOX6 was inferior to 5-FU/folinic acid).
- 6.24 The ESC noted that the naïve indirect comparison of irinotecan (nanoliposomal) and oxaliplatin-containing regimens based on the NAPOLI-1 trial and meta-analysis of the CONKO-003 and PANCREOX trials was largely uninformative given the major issues of applicability, heterogeneity and exchangeability.

Comparative harms



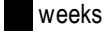





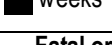
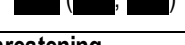





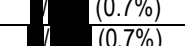



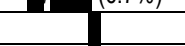







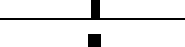








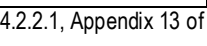
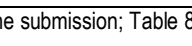
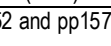
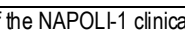
- 6.25 Direct comparison with 5-FU/folinic acid: Irinotecan (nanoliposomal) was associated with a higher incidence of severe or life-threatening treatment-related adverse events (primarily gastrointestinal toxicity, neutropenia, fatigue and decreased appetite) and reports of treatment-related deaths (neutropenic sepsis) compared with 5-FU/folinic acid. Overall, there was a significantly higher incidence of all treatment-related adverse events (for all severities) in patients receiving irinotecan (nanoliposomal) compared with 5-FU/folinic acid that could substantially affect patients' quality of life.

- 6.26 Indirect comparison with oxaliplatin-containing regimens: The submission presented a naïve indirect comparison of irinotecan (nanoliposomal) with oxaliplatin-containing regimens using safety data from the NAPOLI-1 trial post-hoc analysis and a pooled safety analysis of the CONKO-003 and PANCREOX trials. The comparison was largely uninformative given the limited documentation available from the CONKO-003 publication and PANCREOX abstract. Furthermore, there were major concerns of heterogeneity between the CONKO-003 and PANCREOX trials and a lack of exchangeability with the NAPOLI-1 trial.

Benefits/harms




- 6.27 A summary of the comparative benefits and harms for irinotecan (nanoliposomal) versus 5-FU/folinic acid is presented in Table 6.

Table 6: Summary of comparative benefits and harms for irinotecan (nanoliposomal) and 5-FU/folinic acid

Benefits	Irinotecan (nanoliposomal)	5-FU/folinic acid	Absolute Difference	HR (95% CI)
Overall survival				
Died				
Median OS (weeks)				
Progression-free survival				
Progressed or died				
Median PFS (weeks)				
Harms				
	Irinotecan (nanoliposomal)	5-FU/folinic acid	Fatal or life-threatening	
			Irinotecan (nanoliposomal)	5-FU/folinic acid
Diarrhoea				
Nausea				
Vomiting				
Fatigue				
Decreased appetite				
Neutropenia/febrile neutropenia				
Septic shock				

Source: Tables 14.2.1.1 and 14.2.2.1, Appendix 13 of the submission; Table 8-9, p152 and pp157-158 of the NAPOLI-1 clinical study report

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

- 6.28 On the basis of the direct evidence presented in the submission, treatment with irinotecan (nanoliposomal) compared with 5-FU/folinic acid resulted in a statistically significant increase in overall survival (median of approximately  weeks) and progression-free survival (median of approximately  weeks).
- 6.29 On the basis of the direct evidence presented in the submission, for every 100 patients treated with irinotecan (nanoliposomal) compared with 5-FU/folinic acid over a maximum follow-up period of  months, approximately:
- 15 more patients would have a serious (fatal or life-threatening) treatment-related adverse event.
 - 32 more patients would have a treatment-related adverse event of any severity, with diarrhoea, nausea and vomiting being the most common of these adverse events.

- 6.30 The naïve indirect comparison presented in the submission did not allow for a comparison of the benefits and harms of irinotecan (nanoliposomal) and oxaliplatin-containing regimens (FOLFIRINOX, mFOLFOX6).

Clinical claim

- 6.31 Direct comparison with 5-FU/folinic acid: The submission described irinotecan (nanoliposomal) in combination with 5-FU/folinic acid as superior in terms of efficacy and inferior in terms of safety compared with 5-FU/folinic acid. The ESC considered the claim was reasonable but noted that the comparison was largely uninformative if 5-FU/folinic acid is not a relevant comparator.
- 6.32 Irinotecan (nanoliposomal) was associated with significantly higher incidences of severe or life-threatening treatment-related adverse events (primarily gastrointestinal toxicity, neutropenia, fatigue and decreased appetite) compared with 5-FU/folinic acid. In addition, there were reports of irinotecan treatment-related deaths. The significantly higher incidence of treatment-related adverse events of any severity in patients receiving irinotecan (nanoliposomal) compared with 5-FU/folinic acid could substantially affect patients' quality of life. The ESC noted that quality of life is likely to already be limited for a patient with metastatic pancreatic adenocarcinoma.
- 6.33 The PBAC considered that the claim of superior efficacy and inferior safety compared with 5-FU/folinic acid was adequately supported, while noting that 5-FU/folinic acid is rarely used in this setting.
- 6.34 Indirect comparison with oxaliplatin-containing regimens: The submission described irinotecan (nanoliposomal) as superior in terms of efficacy and non-inferior in terms of safety compared with oxaliplatin-containing regimens. The ESC considered this claim was unreasonable in terms of both efficacy and safety.
- 6.35 The results from the meta-analysis of the CONKO-003 and PANCREOX trials comparing oxaliplatin-containing regimens (OFF and mFOLFOX6) with 5-FU/folinic acid were of limited reliability. The trials were not sufficiently comparable with contrasting results (the CONKO-003 trial suggested that the OFF regimen was superior to 5-FU/folinic acid and the PANCREOX trial results indicated that mFOLFOX6 was inferior to 5-FU/folinic acid) as well as differences in the dose strength, frequency and cycles of administration used for each treatment (OFF, mFOLFOX6 and 5-FU/folinic acid arms in both trials). The patient populations in the trials included patients with earlier stage pancreatic cancer, with potentially better survival risk compared with the target population.
- 6.36 The evaluation and the ESC considered that the naïve indirect comparison of irinotecan (nanoliposomal) with oxaliplatin-containing regimens (OFF and mFOLFOX6) was largely uninformative due to significant applicability and heterogeneity issues across the CONKO-003 and PANCREOX trials and exchangeability issues with the NAPOLI-1 trial.
- 6.37 There were limited safety data available from the CONKO-003 and PANCREOX trials. The naïve indirect safety comparison between the pooled analysis and selected data from the NAPOLI-1 trial did not support the claim of non-inferiority in

terms of safety between irinotecan (nanoliposomal) and oxaliplatin-containing regimens. The pre-PBAC response (p2) stated that 5-FU/folinic acid is not likely to be inferior in safety to oxaliplatin-containing regimens on the basis of a comparison of pooled risks of any grade three or higher treatment emergent adverse events in the CONKO-003, PANCREOX, and NAPOLI-1 trials (resulting in a relative risk of ■■■■ for irinotecan (nanoliposomal) versus 5-FU/folinic acid and ■■■■ for oxaliplatin-containing regimens versus 5-FU/folinic acid).

- 6.38 The PBAC considered that in principle (even though it is not widely used in Australian practice), 5 FU/folinic acid could be considered representative of the efficacy and toxicity of mFOLFOX6. Accordingly, the PBAC considered that the claim of superior comparative effectiveness compared with oxaliplatin-containing regimens (OFF and mFOLFOX6) was adequately supported by the data. However, the PBAC considered that the limitations of the naïve indirect comparison meant that confidence about statements of relative efficacy between irinotecan (nanoliposomal) and oxaliplatin-containing regimens was necessarily low.
- 6.39 The PBAC considered that irinotecan (nanoliposomal) is likely to be of similar safety to oxaliplatin-containing regimens (with both regimens having significant toxicities) but may be inferior in safety to some other alternative second-line treatment options.

Economic analysis

- 6.40 The submission presented a modelled cost-utility analysis comparing irinotecan (nanoliposomal) to 5-FU/folinic acid and mFOLFOX6 for the treatment of metastatic pancreatic cancer in patients with disease progression who have previously received gemcitabine-based therapy.
- 6.41 A summary of the model structure and rationale is presented in Table 7.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 2 years in the trial
Outcomes	Quality-adjusted life years, life years
Methods used to generate results	Markov cohort expected value analysis
Treatments	Irinotecan (nanoliposomal) plus 5-FU/folinic acid, 5-FU/folinic acid and mFOLFOX6
Health states	Pre-progression on-treatment, pre-progression off-treatment, post-progression, death
Cycle length	1 week; half-cycle correction applied to outcomes but not costs
Discount rate	5% for costs and outcomes
Transition probabilities	Based on partitioned survival analysis. Progression-free, time on treatment and overall survival probabilities derived from extrapolated survival curves from the NAPOLI-1 trial.
Software package	Excel 2013

Source: constructed during the evaluation

- 6.42 The economic model was based on survival data from the NAPOLI-1 trial without explicit patient characteristics. The modelled population for mFOLFOX6 was synthesised using survival estimates from the 5-FU/folinic acid arm in the model, drug costs using the dosing regimen from eviQ guidelines (which differed to the regimen in the trials), utility values from published literature and adverse event data

from the meta-analysis of the CONKO-003 and PANCREOX trials. The modelled population is unlikely to be applicable to the PBS population.

- 6.43 Given the poor prognosis of the disease and very low five-year survival rates, the ESC considered it was not reasonable to use a time horizon beyond the trial period of two years. A trial-based analysis would have been more appropriate as majority of events were captured by the end of the trial and the survival curves had effectively converged. The pre-PBAC response (p3) argued that a five year time horizon is appropriate to ensure the outcomes and costs of the 5% to 10% of patients with metastatic pancreatic adenocarcinoma who survive longer than two years are captured.
- 6.44 The ESC considered the lack of a relationship between overall survival, progression-free survival and time on treatment in the model could result in invalid sensitivity analyses due to the possibility of logical clinical relationships between the parameters not being maintained.
- 6.45 The key drivers of the model were the extrapolated survival and time on treatment estimates, and utility estimates (baseline and adverse event utility decrement) as summarised in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Extrapolation of survival and progression free survival	Extrapolation to 5 years using 2 years trial data. Majority of events were captured by the end of the trial and the survival curves had effectively converged.	High, favours irinotecan (nanoliposomal)
Baseline utility estimates	Pre-progression (on-treatment and off-treatment states), 0.80; Post-progression, 0.75 from Romanus et al (2012)	High, favours irinotecan (nanoliposomal)
AE utility decrements (base case)	Excluded from base case analysis.	High, favours irinotecan (nanoliposomal)
AE utility decrements (sensitivity analysis)	Selection of adverse events (assumption) with utility decrements from published literature not specific to pancreatic cancer; adjusted by adverse event incidence and treatment exposure time	Unclear
Treatment costs	Predicted > observed time off treatment in pre-progression state.	High, favours irinotecan (nanoliposomal)
Post-progression costs	Differential post-progression irinotecan (nanoliposomal) costs applied to treatment and comparator arms.	Moderate, favours irinotecan (nanoliposomal)

Source: constructed during the evaluation

- 6.46 The transition probabilities used in the model were based on extrapolated overall survival and progression-free survival from the NAPOLI-1 trial (post-hoc analysis). The source of data used to inform the modelled time on treatment estimates could not be validated due to poor documentation in the submission. In the model, progression-free survival estimates were higher and time on treatment estimates were lower compared with trial data. The use of modelled estimates increased the proportion of patients who remained in the pre-progression off-treatment state who maintained treatment benefit without accruing drug costs. This approach favoured

irinotecan (nanoliposomal) as the incremental cost was primarily driven by drug costs.

- 6.47 There was limited justification to support the baseline utilities applied to the pre-progression (on-treatment and off-treatment) and post-progression states. The utility values used (pre-progression states = 0.8; post-progression state = 0.75) may not be representative of the target population. The ESC noted that patients in the pre-progression health state still have metastatic pancreatic cancer and the specified utility values are inappropriately similar to those of the general population of the same age. Other studies suggested considerably lower values of between 0.6 and 0.7 for metastatic pancreatic cancer (e.g. Heiberg 2013, Ljungman 2013 and Müller-Nordhorn 2006 using UK tariffs).
- 6.48 There was inadequate justification for not including the adverse event utility decrement in the base case. The PSCR noted that the baseline utility values were considered to include treatment-related adverse events, although this assumption was in contrast with the same utility value being applied to both pre-progression states (on-treatment and off-treatment) regardless of treatment status. The PSCR noted that the submission presented the results with utility decrements included and that the inclusion demonstrated a moderate impact on the ICER (see Step 5 in Table 9).
- 6.49 The selection of adverse events used to estimate utility decrements did not reflect the full list of treatment-related adverse events reported in the trial. The approach used to adjust the utility decrements for treatment exposure time was also inconsistent with the costing approach; utility decrements were adjusted based on adverse event incidence and treatment exposure time whereas cost of treating adverse events was based on adverse event duration and exposure. Due to insufficient documentation, the source of data used to inform adverse event duration and exposure could not be validated.
- 6.50 In addition, post-progression treatment costs were highly uncertain as the costs relied on the unreasonable assumption that any patient receiving post-progression anti-cancer therapy would be treated with irinotecan (nanoliposomal) monotherapy (not being considered for TGA approval) which was inconsistent with the draft product information and the proposed PBS restriction (cease therapy upon disease progression). The PSCR (p5) agreed 'that the selection of irinotecan (nanoliposomal) monotherapy for post-progression treatment in a subset of patients may not be representative of all possible therapies or regimens used in patients with disease progression', where 'the true post-progression treatment cost may be greater than or less than the assumed irinotecan (nanoliposomal) treatment'.
- 6.51 Post-progression treatment costs assumed ■% and ■% of irinotecan (nanoliposomal) and comparator patients, respectively, incur \$■ weekly irinotecan (nanoliposomal) treatment cost post-progression. The ESC considered that the differential application of treatment costs was inadequately justified.
- 6.52 The results of the stepped economic evaluation comparing irinotecan (nanoliposomal) and 5-FU/folinic acid are summarised in Table 9.

Table 9: Results of the stepped economic evaluation (irinotecan (nanoliposomal) versus 5-FU/folinic acid)

Step and component	Irinotecan (nanoliposomal)	5-FU/folinic acid	Increment
Step 1: Trial-based analysis, based on 2-year trial data for survival and treatment exposure time plus drug and administration costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Step 2: Trial-based analysis, based on 2-year trial data for survival and treatment exposure time plus monitoring and adverse event costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Step 3a: Modelled analysis, 2 year duration, treatment exposure time from modelled estimates plus all costs (drug, administration, monitoring, adverse event, post-progression treatment and last 4 weeks of life cost) – calculated during the evaluation			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Step 3b: Modelled analysis, 3 year duration, treatment exposure time from modelled estimates plus all costs (drug, administration, monitoring, adverse event, post-progression treatment and last 4 weeks of life cost)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Step 4: Modelled analysis, 5 year duration			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Step 5: Modelled analysis, 5 year duration with baseline utilities and adverse event utility decrement			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 6: Modelled analysis, 5 year duration with baseline utilities and no adverse event utility decrement			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Table D.5.13, p215 and 'ONIVYDE PBAC Model_final version for analyses_final' Excel Workbook, Appendix 19 of the submission

Abbreviations: LY, life years; QALY, quality-adjusted life years

- 6.53 Based on the economic model, treatment with irinotecan (nanoliposomal) was associated with an incremental cost of \$75,000 - \$105,000 per QALY gained compared with 5-FU/folinic acid. The ESC noted that the trial based analysis (step 2 in Table 9) had an incremental cost of \$105,000 - \$200,000 per life year gained. However, the ESC considered these results were not informative if 5-FU/folinic acid is not a relevant comparator.
- 6.54 Results from the stepped analysis suggested that the ICER was most sensitive to the switching from trial data to modelled estimates plus the addition of all relevant costs. The ICER was also sensitive to the addition of baseline utilities and adverse event utility decrements.

- 6.55 The results of the economic evaluation comparing irinotecan (nanoliposomal) and mFOLFOX6 are summarised in Table 10.

Table 10: Results of the economic evaluation (irinotecan (nanoliposomal) versus mFOLFOX6

Component	Irinotecan (nanoliposomal)	mFOLFOX6	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Lys	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained (base case)			\$ [REDACTED]
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs (with AE decrements)	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Tables D.5.4 and D.5.6, pp210-211 and 'ONIVYDE PBAC Model_final version for analyses_final' Excel workbook
Abbreviations: AE, adverse event; LYs, life years; QALYs, quality-adjusted life years

- 6.56 Based on the economic model, treatment with irinotecan (nanoliposomal) was associated with an incremental cost per QALY gained of \$105,000 - \$200,000 compared with mFOLFOX6 (including utility decrements for treatment-related adverse events).
- 6.57 The estimated ICERs should not be considered reliable given the major concerns regarding issues with the model structure (inflation of time spent in the pre-progression off-treatment state), unnecessary extrapolation of survival (as majority of events were captured by the end of the trial and the survival curves had effectively converged), highly uncertain utility values and issues of applicability of the synthesised population to the proposed PBS population for the mFOLFOX6 comparison. The economic model was sensitive to survival curves, utility values, drug costs and post-progression treatment costs.
- 6.58 The pre-PBAC response (p3) provided three alternative base case ICERs to individual examine the impact of a reduction in the modelled time horizon, an increase in the cost of comparative treatments and a reduction in the utility values for the pre and post-progression health states. The redacted table below shows that all of the alternative ICERs presented in the pre-PBAC response were \$105,000 - \$200,000 per QALY. The pre-PBAC response claimed that these changes demonstrated the robustness of the model; however, the response did not present a revised ICER with all three changes combined, or with a trial based analysis as recommended by ESC.

Table 11: Alternative ICERs presented in the pre-PBAC response

Change to the model	ICER per QALY vs. 5-FU/LV	ICER per QALY vs. mFOLFOX6
Two year modelled time horizon	\$ [REDACTED]	\$ [REDACTED]
Increase in price of 5-FU/LV and mFOLFOX6	\$ [REDACTED]	\$ [REDACTED]
Utility estimates to reflect the lower end of the range of published estimates (0.70 and 0.65)	\$ [REDACTED]	\$ [REDACTED]

Source: Pre-PBAC response, Table 1.

Drug cost/patient/6 weeks: \$ [REDACTED]

- 6.59 The cost per patient every 6 weeks (3 cycles, 3 administrations) for irinotecan (nanoliposomal) in combination with 5-FU/folinic acid is approximately \$ [REDACTED] (Section 100, Efficient Funding of Chemotherapy dispensed price). This was calculated using the proposed effective dispensed price and assuming the average body surface area of 1.8 m² for a patient, requiring 144 mg of irinotecan (nanoliposomal) (3 × 50 mg vials), 720 mg of folinic acid (average cost per mg of \$0.08 using DPMQ for 50 mg vial) and 4320 mg of 5-FU (2 × 1,000 mg and 1 × 2,500 mg vials). The submission assumed that [REDACTED]% of the drug would be dispensed in public hospitals and [REDACTED]% in private hospitals. The price was not adjusted for relative dose intensity as applied in the economic model.
- 6.60 The cost of 6 weeks of the irinotecan (nanoliposomal) regimen was compared with a cost of \$712 for treatment with 5-FU/folinic acid (1 cycle, 4 administrations) and \$1,233 for the mFOLFOX6 regimen (3 cycles, 3 administrations).

Estimated PBS usage & financial implications

- 6.61 The submission was considered by DUSC. An epidemiological approach based on disease incidence was adopted by the submission. The submission stated that incidence rather than prevalence was used to reflect the low median survival for patients with metastatic pancreatic cancer. DUSC considered an incidence approach was appropriate. At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 - \$20 million (using the updated estimates in the PSCR, see Table 12).
- 6.62 The DUSC considered the estimates presented in the submission to be underestimated. The main issues were:
- Uptake will be affected by how clinicians interpret the trial data with regards to clinical effect and the side effect profile.
 - Due to the poor overall outcome of treatment for pancreatic cancer, and the lack of clear superiority of one regimen over another, it is likely that multiple lines of therapy may be trialled.
 - Uptake and market share might be affected if newer agents for pancreatic cancer become available in the near future due to the number of clinical trials underway in this area.
 - Drug costs, administration costs and monitoring costs have been imported from the economic model and incorporated all key issues of uncertainty such as modelled survival estimates, time on treatment and costing methods.
 - Whether it was reasonable to use the mFOLFOX6 regimen as a proxy for all treatment regimens likely to be substituted given the wide range of treatment options that could be cheaper or more expensive than the mFOLFOX6 regimen.
- 6.63 The DUSC had also considered that estimated financial implications are likely to be underestimated as the submission did not account for treatment of patients who may have recurrence after diagnosis with early stage pancreatic cancer without resection and those with complete resection. However, the PSCR response had provided revised estimates to address this matter and these revised estimates were again presented in the pre-PBAC response.

Table 12: Estimated utilisation and cost to the PBS in the first five years of listing based on proposed effective price

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Australian population	24,781,121	25,201,317	25,619,895	26,037,356	26,452,147
Incidence of pancreatic cancer (13 cases: 100,000 population)	3,238	3,335	3,434	3,534	3,636
Metastatic adenocarcinoma (at diagnosis and after resection)	1,847	1,902	1,959	2,016	2,074
Patients previously on first-line gemcitabine-based therapy and start second-line chemotherapy	■	■	■	■	■
- Uptake rate of irinotecan (nanoliposomal)	■%	■%	■%	■%	■%
- Patients on second-line irinotecan (nanoliposomal)	■	■	■	■	■
Second-line patients who progress and start third-line chemotherapy	■	■	■	■	■
- Uptake rate of irinotecan (nanoliposomal)	■%	■%	■%	■%	■%
- Patients on third-line irinotecan (nanoliposomal)	■	■	■	■	■
Total treated patients	■	■	■	■	■
Revised total treated patients (PSCR p7)	■	■	■	■	■
Cost of irinotecan (nanoliposomal)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost of concomitant 5-FU	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost of concomitant folinic acid	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Total cost of treatment regimen (based on total drug cost in the economic model)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Patient co-payments (one co-payment of \$20.11 per drug per patient)	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Cost of substituted mFOLFOX6 regimen (based on total drug cost in the economic model minus one co-payment of \$20.11 per drug per patient)	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Net cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Revised net cost to PBS/RPBS (PSCR p7)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Costs of administration and monitoring (based on incremental difference compared with mFOLFOX6 in the economic model)	\$932,658	\$1,347,977	\$1,734,922	\$2,036,246	\$2,352,457
Total cost to government	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Revised total cost to government (PSCR p7)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table 11, page 15 of Commentary with updated estimates from the PSCR, page 7

6.64 The pre-PBAC response stated that the revised estimates in the PSCR are the upper limit of the potential budget impact for irinotecan (nanoliposomal).

Financial Management – Risk Sharing Arrangements

6.65 The sponsor proposed a special pricing arrangement based on a [REDACTED] % rebate of the proposed published ex-manufacturer price for each vial of irinotecan (nanoliposomal). The proposed effective DPMA (maximum amount of 200 mg) is summarised in the table below.

Table 12: Proposed special pricing arrangement

	Published	Effective
Proposed AEMP	\$ [REDACTED]	\$ [REDACTED]
DPMA (Public)	[REDACTED]	[REDACTED]
DPMA (Private)	\$ [REDACTED]	\$ [REDACTED]

Source: p15 of the submission

Abbreviations: AEMP, agreed ex-manufacturer price, DPMA, dispensed price maximum amount

Note: The proposed prices were estimates based on ex-manufacturer price (and 1.4% mark-up for private hospital) and efficient funding of chemotherapy fees as of 1 July 2015. There was a slight increase in efficient funding of chemotherapy fees from 1 July 2016 that would have minimal impact on the economic analysis and financial estimates.

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 irinotecan (in the form of I.V. injection containing nanoliposomal irinotecan 43 mg in 10 mL, referred to as irinotecan (nanoliposomal)) in combination with 5-FU/folinic acid for the treatment of metastatic pancreatic adenocarcinoma in adult patients with disease progression who have previously received gemcitabine-based therapy. This decision was made on the basis of an unacceptably high incremental cost for a modest and uncertain incremental clinical benefit.

7.2 The PBAC noted and welcomed the consumer comments received relating to this submission, including from the Medical Oncology Group of Australia, Pancare Foundation and Rare Cancers Australia via the Consumer Comments facility on the PBS website. The PBAC acknowledged the high clinical need for effective and well-tolerated therapies for metastatic pancreatic adenocarcinoma, particularly in the context of the poor prognosis for this condition.

7.3 The PBAC noted and accepted the submission’s proposed clinical place for irinotecan (nanoliposomal) as an alternative treatment in patients with metastatic pancreatic adenocarcinoma who have disease progression after previous treatment with gemcitabine-based therapy. The PBAC noted that irinotecan (in the form of I.V. injection containing irinotecan hydrochloride trihydrate 500 mg in 25 mL) has an unrestricted Section 100 (Efficient Funding of Chemotherapy) listing. The submission did not request, or provide evidence to support, PBS-subsidised use of irinotecan (nanoliposomal) either as a replacement for irinotecan in irinotecan-containing therapies, such as FOLFIRINOX, nor for use following treatment with irinotecan-containing therapies.

7.4 In the requested setting, the PBAC considered that the most relevant comparators are oxaliplatin-containing regimens (such as mFOLFOX6) and capecitabine, with FOLFIRINOX only used in a small number of patients. The PSCR and pre-PBAC

response stated that expert opinion affirmed that 5-FU/folinic acid is representative of the range of therapies (including fluoropyrimidine-based comparators such as capecitabine) that are used in the proposed target patient population. The PBAC considered that in principle (even though it is not widely used in Australian practice), 5-FU/folinic acid could be considered representative of the efficacy and toxicity of mFOLFOX6.

- 7.5 The PBAC noted the submission was primarily based on one head-to-head, open label trial comparing irinotecan (nanoliposomal) with 5-FU/folinic acid: NAPOLI-1 (n=236). The PBAC noted this trial was considered during the evaluation to have a high risk of bias (see paragraph 6.7). The PBAC considered that irinotecan (nanoliposomal) was modestly superior in terms of efficacy compared with 5-FU/folinic acid, with an increase in median overall survival of approximately nine weeks. The PBAC noted that after a median follow-up period of [REDACTED] weeks, [REDACTED]% of patients in the irinotecan (nanoliposomal) treatment group had died, compared with [REDACTED]% of patients in the 5-FU/folinic acid group.
- 7.6 The submission also presented a naïve indirect comparison of irinotecan (nanoliposomal) versus 5-FU/folinic acid (NAPOLI-1) with a meta-analysis of oxaliplatin-containing regimens (OFF and mFOLFOX6) versus 5-FU/folinic acid (CONKO-003 (n=126) and PANCREOX (n=108)). The PBAC noted the issues raised by the ESC that limited the reliability of the indirect comparison; these included the high risk of bias of all three trials, applicability to Australian clinical practice, heterogeneity across CONKO-003 and PANCREOX, and exchangeability of the NAPOLI-1 and meta-analysed trials (see paragraphs 6.7 to 6.10). The PBAC noted the argument in the pre-PBAC response (p1-2) that the usefulness of the naïve indirect meta-analysis evidence should be considered in the context of an uncommon disease with high clinical need and poor prognosis. The PBAC agreed with the ESC that the results of the naïve indirect comparison were not reliable, but overall considered that the claim of superior comparative effectiveness, compared with oxaliplatin-containing regimens, was adequately supported. The PBAC considered that the limitations of the comparisons meant that confidence about statements of relative efficacy between irinotecan (nanoliposomal) and oxaliplatin-containing regimens was necessarily low. The PBAC considered the incremental benefit of irinotecan (nanoliposomal) over 5-FU/folinic acid observed in NAPOLI-1 ([REDACTED] week gain in overall survival) to be the upper limit of a plausible incremental benefit of irinotecan (nanoliposomal) over oxaliplatin-containing regimens.
- 7.7 The PBAC agreed with the submission that irinotecan (nanoliposomal) is inferior in terms of safety compared with 5-FU/folinic acid. The PBAC considered that irinotecan (nanoliposomal) is likely to be of similar safety to oxaliplatin-containing regimens (with both regimens having significant toxicities) but may be inferior in safety to some other alternative second-line treatment options.
- 7.8 The PBAC noted that the submission presented a modelled cost-utility analysis comparing irinotecan (nanoliposomal) to 5-FU/folinic acid and mFOLFOX6. The PBAC agreed with the ESC that a trial-based analysis was more appropriate for decision making in this instance, given the maturity of the clinical data where the majority of events were captured before the end of the trial. In addition, the PBAC considered the following issues with the model may have resulted in the ICER per QALY for irinotecan (nanoliposomal) being underestimated:

- Compared with the trial data, the model overestimated the time spent in the pre-progression off-treatment state, with patients maintaining treatment benefit without the accrual of drug costs, monitoring costs and administration costs.
- The costing assumptions inflated the prices of the 5-FU/folinic acid and mFOLFOX6 regimens relative to irinotecan (nanoliposomal).
- The utility estimates for pre-progression (0.8) and post-progression (0.75) were similar to those of the general population of the same age, and therefore were inappropriately high for patients with metastatic pancreatic cancer. In addition, the submission base case did not include utility decrements for treatment-related adverse events.
- The differential application of post-progression irinotecan (nanoliposomal) treatment costs was inadequately justified.

7.9 Notwithstanding the above issues, the PBAC noted that the base case ICER in the submission and the alternative ICERs in the pre-PBAC response were over \$100,000 per QALY gained. Accordingly, the PBAC considered that irinotecan (nanoliposomal) was not sufficiently cost-effective to justify a recommendation for listing on the PBS, at the requested price.

7.10 The PBAC recommended that a resubmission should present the cost-effectiveness of irinotecan (nanoliposomal) compared with mFOLFOX6, using the trial results compared with 5-FU/folinic acid from NAPOLI-1 as a proxy for the incremental benefit over oxaliplatin-containing regimens, and address other issues identified with the model (see paragraph 7.8). The PBAC considered that a significant reduction in the requested price would be required to provide greater confidence in the cost-effectiveness of irinotecan (nanoliposomal), particularly in the context of the modest and uncertain incremental benefit compared with oxaliplatin-containing regimens. In this regard, the PBAC considered that the revised base case ICER should not exceed \$50,000 per QALY gained.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Shire will work with the PBAC and Department of Health so that Australian patients may access nanoliposomal irinotecan via the PBS.