

7.04 IRINOTECAN (NANOLIPOSOMAL), 43 mg in 10 mL Injection, ONIVYDE[®], Shire Australia Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy) Streamlined Authority Required listing for irinotecan (nanoliposomal) in combination with 5-fluorouracil (5-FU) and folinic acid for the treatment of patients with metastatic pancreatic adenocarcinoma who have previously failed gemcitabine-based therapy.
- 1.2 Irinotecan (nanoliposomal) plus 5-FU/folinic acid was previously considered by the PBAC in November 2016.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis compared with mFOLFOX6 (oxaliplatin plus 5-FU/folinic acid) using 5-FU/folinic acid monotherapy as a proxy.
- 1.4 Any further reference to irinotecan (nanoliposomal) will describe the drug component whereas the irinotecan (nanoliposomal) plus 5-FU/folinic acid regimen will be described as nal-IRI.

Table 1: Key components of the clinical issue addressed in the submission

| Component | Description |
|----------------|--|
| Population | Patients with metastatic pancreatic adenocarcinoma who have previously failed gemcitabine-based therapy. |
| Intervention | Irinotecan (nanoliposomal) plus 5-fluorouracil/folinic acid |
| Comparator | mFOLFOX6 (oxaliplatin plus 5-fluorouracil/folinic acid) |
| Outcomes | Improvement in survival and delay in disease progression |
| Clinical claim | Irinotecan (nanoliposomal) plus 5-fluorouracil/folinic acid is superior in terms of efficacy and similar in terms of safety compared with mFOLFOX6 |

Source: Table 1.1-1, p5 of the submission

Abbreviations: ECOG, Eastern Cooperative Oncology Group

2 Requested listing

- 2.1 Key differences compared with the requested listing in the November 2016 submission were the addition of clinical criteria that restricts the use of irinotecan (nanoliposomal) to patients with no prior exposure to irinotecan (non-nanoliposomal), and that patients must have an ECOG performance status score of 0 to 2.

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

| Name, Restriction, Manner of administration and form | Max. Amt | No. of Rpts | Dispensed Price for Max. Amt | Proprietary Name and Manufacturer |
|---|----------|-------------|--|------------------------------------|
| IRINOTECAN-NANOLIPOSOMAL 43 mg/10 mL injection, 10 mL vial | 160mg | 11 | \$ [REDACTED] (Public) \$ [REDACTED] (Public)* \$ [REDACTED] (Private) \$ [REDACTED] (Private)* | Onivyde Shire Australia Pty Ltd |

*Effective prices

| | |
|------------------------------------|--|
| Category / Program | Section 100 – Efficient funding of Chemotherapy |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Episodicity: | - |
| Severity: | Stage IV (metastatic) |
| Condition: | Adenocarcinoma of the pancreas |
| PBS Indication: | Stage IV (metastatic) adenocarcinoma of the pancreas |
| Treatment phase: | Initial treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Treatment criteria: | The treatment must be in combination with 5 fluorouracil and folinic acid. |
| Clinical criteria: | <p><i>The treatment must be in combination with 5-fluorouracil and folinic acid</i></p> <p>AND</p> <p>The condition must have progressed following treatment with gemcitabine-based therapy</p> <p>AND</p> <p>The patient must not have received treatment with irinotecan</p> <p><i>Patient must not have previously received this drug for this condition,</i></p> <p>AND</p> <p>The p Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less.</p> |

| | |
|------------------------------|---|
| Population criteria: | A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. |
| Administrative Advice | A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. Special Pricing Arrangements apply. |

- 2.3 The Pre-Sub-Committee Response (PSCR), proposed an amendment to the requested listing to include all patients with metastatic pancreatic cancer who have previously failed gemcitabine regardless of prior irinotecan exposure. This is consistent with the TGA approved indication. The ESC also noted that while the irinotecan exposed subgroup showed no evidence of effect of nal-IRI (OS HR (95% CI) for nal-IRI versus 5-FU/folinic acid: [REDACTED] ([REDACTED])), this constituted only 12% of patients in the pivotal trial and the test for interaction for the pre-specified ITT subgroup analysis (data cut-off 14 February 2014) indicated that prior irinotecan exposure was not a treatment effect modifier. The ESC considered removal of this criterion to be appropriate.
- 2.4 The PSCR (p4), proposed an amendment to the requested listing to remove the requirement for an Eastern Cooperative Oncology Group (ECOG) score of less than 2. The ESC noted that there was variability in mapping the Karnofsky Performance Score (KPS) used in the trial to ECOG performance status (PS), but that most patients in the trial would have had an ECOG PS of 1 or less. The ESC therefore considered that it would be appropriate for the decision to treat with nal-IRI in patients with an ECOG score of ≥ 2 to be a clinical practice decision, made in consultation with patients. The ESC also considered that such patients would unlikely be treated with nal-IRI due to the associated toxicities and because international treatment guidelines recommend treatment in patients with good performance status (ECOG 0-1).
- 2.5 The resubmission proposed a special pricing arrangement based on a [REDACTED]% rebate applied to the published AEMP per vial (43 mg irinotecan in free base form, 50 mg as irinotecan hydrochloride trihydrate; dosing based on free base form) of \$[REDACTED]. This corresponds to an effective AEMP of \$[REDACTED]. The corresponding public and private hospital prices (published and effective) were calculated assuming 4 vials are required to administer a maximum amount of 160 mg (assuming 43 mg per vial, and dosing of 70mg/m² with max BSA of 2.2m²). The proposed special pricing arrangement is unchanged from the November 2016 submission.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Background

Registration status

3.1 Irinotecan (nanoliposomal) was approved by the TGA on 19 December 2016 for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and folinic acid (leucovorin) in adult patients who have been previously treated with gemcitabine-based therapy.

Previous PBAC consideration

3.2 The outstanding matters of concerns from the November 2016 PBAC meeting are summarised in the table below. The resubmission provided additional follow-up data (to three years) for the NAPOLI-1 trial, and a trial-based economic evaluation based on these data. The requested price for nal-IRI remained unchanged.

Table 2: Comparison of the November 2016 submission and this resubmission

| Component | November 2016 submission and PBAC view | Current resubmission |
|---------------------|---|--|
| Requested listing | Metastatic pancreatic adenocarcinoma patients who have failed gemcitabine-based therapy. | Metastatic pancreatic adenocarcinoma patients who have failed gemcitabine-based therapy. No prior exposure to irinotecan. Performance status based on ECOG 0-2 |
| Proposed price | DPMA for 160 mg (4 vials): Published price - \$ [redacted] (public) - \$ [redacted] (private) Effective price - \$ [redacted] (Public) - \$ [redacted] (Private) | Same as November 2016 submission |
| Comparators | 5-FU/folinic acid and mFOLFOX6 | mFOLFOX6 |
| Basis of comparison | One head-to-head trial comparing nal-IRI with 5-FU/folinic acid (NAPOLI-1). A naïve indirect comparison of nal-IRI (NAPOLI-1) with oxaliplatin-containing regimens (CONKO-003 and PANCREOX) [7.6] The PBAC noted that the results of the naïve indirect analyses comparing nal-IRI with oxaliplatin-containing regimens were not reliable | No indirect analyses were presented in the resubmission One head-to-head trial comparing nal-IRI with 5-FU/folinic acid (NAPOLI-1) as a proxy for mFOLFOX6, with additional subgroup analysis by prior irinotecan exposure |
| Clinical claim | Nal-IRI is superior in terms of efficacy and inferior in terms of safety compared with 5-FU/folinic acid. Nal-IRI is superior in terms of efficacy and non-inferior in terms of safety compared with oxaliplatin-containing regimens. [7.6] The PBAC considered that the claim of superior comparative effectiveness, compared with oxaliplatin-containing regimens was adequately supported but that the limitations of the comparisons meant that confidence about statements of relative efficacy between nal-IRI and oxaliplatin-containing regimens was necessarily low | Nal-IRI is superior in terms of efficacy and non-inferior safety compared with mFOLFOX6 The resubmission assumed that data from the 5-FU/folinic arm of the NAPOLI-1 trial could be used as a proxy for mFOLFOX6 in terms of both efficacy and safety. The resubmission did not explore the impact of smaller incremental benefits with nal-IRI compared to mFOLFOX6. |

Public Summary Document – March 2018 PBAC Meeting

| Component | November 2016 submission and PBAC view | Current resubmission |
|---------------------|--|---|
| | The PBAC considered the incremental benefit of nal-IRI over 5 FU/folinic acid observed in NAPOLI-1 (nine week gain in overall survival) to be the upper limit of a plausible incremental benefit of nal-IRI over oxaliplatin-containing regimens. | |
| Model structure | <p>Partitioned survival analysis with 4 health states:</p> <ul style="list-style-type: none"> - pre-progression on-treatment - pre-progression off-treatment - post-progression - death <p>Survival probabilities derived from extrapolated survival curves (overall survival, progression-free survival, time on treatment). Time horizon of 5 years with weekly cycle length</p> <p>[7.8] The PBAC noted that a trial-based economic 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.</p> <p>[7.8] 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.</p> <p>[7.10] The PBAC recommended that a resubmission should present the cost-effectiveness of nal-IRI 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</p> | <p>The resubmission presented a trial-based economic analysis based on the NAPOLI-1 trial (and irinotecan naïve subgroup)</p> <p>Same model structure and health states based on partitioned survival analysis derived from trial-based survival curves (overall survival, progression-free survival, time to treatment failure). Time horizon of 3 years with weekly cycle length</p> <p>The time spent in the pre-progression off treatment state was based on trial data in the resubmission. However, the resubmission continued to assume that this group of patients maintain treatment benefit without any further costs</p> |
| Outcomes | Quality-adjusted life years, life years | Life years |
| Model inputs | <p>Nal-IRI vs 5-FU/folinic acid comparison based on trial data</p> <p>Nal-IRI vs mFOLFOX6 comparison used trial-based model inputs, assuming efficacy data from the 5-FU/folinic acid monotherapy arm was a proxy for mFOLFOX6</p> <p><u>Data source:</u> OS and PFS survival curves derived from post-hoc analyses of ITT population (NAPOLI-1). Inadequate detail provided to determine source data for time on treatment survival curve.</p> | <p>Nal-IRI vs mFOLFOX6 (using 5-FU/folinic acid as a proxy) comparison based on trial data</p> <p><u>Data source:</u></p> <ul style="list-style-type: none"> - Base case: OS, PFS and time on treatment survival curves derived from updated post-hoc analysis of irinotecan naïve patient subgroup (NAPOLI-1) - Alternative: OS, PFS and time on treatment survival curves derived from updated post-hoc analysis of ITT population (NAPOLI-1) |
| Drug costs per week | <p>Effective prices September 2016 PBS schedule</p> <p>Nal-IRI: \$ [REDACTED]</p> <p>5-FU/folinic acid: \$ [REDACTED]</p> <p>mFOLFOX6: \$ [REDACTED]</p> | <p>Effective prices December 2017 PBS schedule</p> <p>Irinotecan naïve subgroup</p> <p>Nal-IRI: \$ [REDACTED]</p> <p>mFOLFOX6: \$ [REDACTED]</p> |

Public Summary Document – March 2018 PBAC Meeting

| Component | November 2016 submission and PBAC view | Current resubmission |
|--|--|--|
| | [7.8] The costing assumptions inflated the prices of the 5-FU/folinic acid and mFOLFOX6 regimens relative to nal-IRI. | ITT population Nal-IRI: \$ [REDACTED] mFOLFOX6: \$ [REDACTED] |
| Administration costs per cycle | Nal-IRI: \$257.29 5-FU/folinic acid: \$326.99 mFOLFOX6: \$257.29 | Lower administration costs for nal-IRI and higher post-progression administration costs. This favours nal-IRI. Nal-IRI: \$81.60 mFOLFOX6: \$81.60 FOLFIRINOX: \$130.58 |
| Adverse event costs per cycle | Nal-IRI: \$42.64 5-FU/folinic acid: \$21.69 mFOLFOX6: \$54.03 | Nal-IRI: \$25.03 mFOLFOX6: \$6.24 |
| Monitoring costs per cycle | Initial monitoring cost (once-off, applied to all): \$350.38 Cost per cycle (all arms): \$104.85 | Initial monitoring cost (once-off, applied to all): \$441.47 Cost per cycle (all arms): \$67.28 |
| Post-progression treatment drug cost per cycle | Drug costs based on irinotecan (nanoliposomal) monotherapy and proportion receiving treatment. Nal-IRI: \$ [REDACTED] 5-FU/folinic acid: \$ [REDACTED] mFOLFOX6: \$ [REDACTED] [7.8] The differential application of post-progression irinotecan (nanoliposomal) [monotherapy] treatment costs was inadequately justified. | The utilisation of subsequent line therapies remained unchanged in the resubmission but the costs of subsequent line treatment were decreased (due to the assumption of FOLFIRINOX being used as a third line treatment) Drug costs based on FOLFIRINOX regimen and proportion starting treatment. Nal-IRI: \$ [REDACTED] mFOLFOX6: \$ [REDACTED] The ESC noted that patients are assumed to stay on treatment until they die, which favours nal-IRI as more patients in the comparator arm commence therapy post-progression. |
| Last 4 weeks of life | \$3,597.06 | Not used |
| Utility/disutility values | Pre-progression on-treatment: 0.80 Pre-progression off-treatment: 0.80 Post-progression: 0.75 <u>Pre-progression total adverse events disutility</u> Nal-IRI: -0.0172 5-FU/folinic acid: -0.0064 mFOLFOX6: -0.0097 <u>Post-progression total adverse events disutility</u> Nal-IRI: -0.0521 5-FU/folinic acid: -0.0210 mFOLFOX6: -0.0254 Adverse event disutilities adjusted by trial-based adverse event durations and exposure data (NAPOLI-1) [7.8] The utility estimates for pre-progression and | The economic model presented in the resubmission was based on survival data only and did not include utility estimates. |

| Component | November 2016 submission and PBAC view | Current resubmission |
|-----------------------------|--|--|
| | post-progression 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. | |
| Economic results | <p>Treatment with nal-IRI was associated with costs per QALY gained of \$ [REDACTED] compared with 5-FU/folinic acid and \$ [REDACTED] compared with mFOLFOX6 in patients with metastatic pancreatic adenocarcinoma who have failed gemcitabine-based therapy.</p> <p>Treatment with nal-IRI was associated with costs per LY gained of \$ [REDACTED] compared with 5-FU/folinic acid and \$ [REDACTED] compared with mFOLFOX6 in patients with metastatic pancreatic adenocarcinoma who have failed gemcitabine-based therapy.</p> <p>[7.9] The PBAC noted that the base case ICER in the submission and the alternative ICERs in the pre-PBAC response were over \$ [REDACTED] 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.</p> <p>[7.10] The PBAC considered that a significant reduction in the requested price would be required to provide greater confidence in the cost-effectiveness of nal-IRI, 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 \$ [REDACTED] per QALY gained.</p> | <p>The price of irinotecan (nanoliposomal) remained unchanged in the resubmission.</p> <p>Treatment with nal-IRI was associated with costs per LY gained of \$ [REDACTED] compared with mFOLFOX6 in the <u>irinotecan naïve subgroup</u> of patients with metastatic pancreatic adenocarcinoma who have failed gemcitabine-based therapy.</p> <p>Treatment with nal-IRI was associated with costs per LY gained of \$ [REDACTED] compared with mFOLFOX6 in patients with metastatic pancreatic adenocarcinoma who have failed gemcitabine-based therapy.</p> |
| Eligible patient population | Revised estimates in PSCR: Metastatic pancreatic adenocarcinoma patients who failed gemcitabine-based therapy: [REDACTED] (Year 1) to [REDACTED] (Year 5) | Metastatic pancreatic adenocarcinoma patients who failed gemcitabine-based therapy, no prior irinotecan, ECOG 0-2: [REDACTED] (Year 1) to [REDACTED] (Year 6) |
| Net cost to PBS | Revised estimates in PSCR: Metastatic pancreatic adenocarcinoma patients who have failed gemcitabine-based therapy: \$ [REDACTED] (Year 1) to \$ [REDACTED] (Year 5) | Metastatic pancreatic adenocarcinoma patients who have failed gemcitabine-based therapy, no prior irinotecan, ECOG 0-2: \$ [REDACTED] (Year 1) to \$ [REDACTED] (Year 6) |

Source: compiled during the evaluation, p 1-5 of the resubmission overview

Abbreviations: DPMA, dispensed price maximum amount; ECOG, Eastern Cooperative Oncology Group performance score; ITT, intent to treat; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

3.3 The most common and aggressive type of pancreatic cancer is adenocarcinoma originating in the pancreatic duct. Pancreatic adenocarcinoma is asymptomatic in early stages and usually 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. Prognosis is poor, with low 5-year survival rates. Based on Australian data provided in the resubmission, patients with pancreatic adenocarcinoma are typically older and at least half are diagnosed with metastatic disease.

- 3.4 In metastatic disease, choice of systemic therapy is influenced by many factors including patient performance status. The resubmission claimed that the majority of patients with metastatic pancreatic cancer are ambulatory (have an ECOG performance status score of 0 to 2). Published guidelines recommend that nal-IRI should be limited to patients with good performance status (ECOG 0-1).
- 3.5 The resubmission positioned nal-IRI as an alternative to a range of therapies including mFOLFOX6 (oxaliplatin plus 5-FU/folinic acid), capecitabine monotherapy, FOLFIRI (irinotecan plus 5-FU/folinic acid), gemcitabine monotherapy, FOLFIRINOX (irinotecan, oxaliplatin, 5-FU/folinic acid) or XELOX (oxaliplatin plus capecitabine) in patients who have failed gemcitabine-based therapy.
- 3.6 The resubmission claimed that the majority of patients who would be eligible for irinotecan (nanoliposomal) would not have prior exposure to irinotecan (non-nanoliposomal). Additionally, the resubmission claimed these patients are likely to derive greater clinical benefit compared to irinotecan experienced patients. This claim was not adequately supported by the data presented in the resubmission (i.e. prior irinotecan exposure may not be a treatment effect modifier for nal-IRI).
- 3.7 The target population for nal-IRI in the resubmission is ambulatory patients with metastatic pancreatic adenocarcinoma who have previously been treated with gemcitabine-based therapy and with no prior exposure to irinotecan. The November 2016 submission did not include restrictions based on performance criteria or prior use of irinotecan.
- 3.8 The PBAC previously accepted the clinical place in therapy for nal-IRI in the context of a broader population in the November 2016 submission, and acknowledged the high clinical need for effective and well-tolerated therapies for this disease, particularly in the context of the poor prognosis for this condition (irinotecan (nanoliposomal) PSD November 2016).

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The resubmission nominated mFOLFOX6 as the main comparator. This was accepted by the PBAC as a relevant comparator in the November 2016 submission in the context of a broader proposed restriction that did not specify patient performance status or prior exposure to irinotecan. The PBAC also considered that the most relevant comparators were oxaliplatin-containing regimens and capecitabine, noting that a small number of patients may use FOLFIRINOX in the requested setting (paragraph 7.4, irinotecan (nanoliposomal) November 2016 PSD).

- 4.2 The resubmission claimed that mFOLFOX6 is commonly used in Australian clinical practice and is the only second line regimen listed in Australian guidelines. However, market data provided in the resubmission suggests that the most commonly used drugs following progression on gemcitabine are capecitabine monotherapy (■%), XELOX (■%), mFOLFOX6 (■%), nab-paclitaxel with/without other chemotherapy (■%), FOLFIRINOX (■%), FOLFIRI (■%), gemcitabine monotherapy (■%) and XELIRI (■%; capecitabine plus irinotecan). This is broadly consistent with recommendations in international guidelines.
- 4.3 Capecitabine monotherapy and XELOX could also be considered alternative comparators as they appear to be commonly used in patients who have failed gemcitabine-based therapy. The ESC noted that the PBAC had previously accepted 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” (Nov 2016 PSD). However, the ESC considered the assessment of cost-effectiveness of nal-IRI for the treatment of this condition should be considered in the context that there are other reasonable alternative comparators that may be less expensive than mFOLFOX6.

For more detail on PBAC’s view, see section 6 PBAC outcome.

5 Consideration of the Evidence

Sponsor hearing

- 5.1 There was no hearing for this item.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (2) via the Consumer Comments facility on the PBS website. The comments described the potential benefits of slowing progression and improving quality of life from treatment with irinotecan (nanoliposomal).
- 5.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the irinotecan (nanoliposomal) submission, on the basis of unmet clinical need after failure of standard prior therapies. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for irinotecan (nanoliposomal) which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with 5-FU.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Clinical trials

- 5.4 The resubmission was based on one head-to-head trial comparing nal-IRI to 5-FU/folinic acid (NAPOLI-1). This trial was previously considered by the PBAC in the November 2016 submission.
- 5.5 The resubmission presented the same clinical data in section 2 of the submission as in the previous submission, but used updated post-hoc analyses from a later data cut of the whole NAPOLI-1 trial population and the irinotecan naïve patient subgroup as clinical inputs in the economic analysis. There was limited information in the resubmission for this data cut-off (follow-up period not reported) although the analysis appeared to include updated individual patient data of up to 3 years, beyond the trial period of 2 years. These data have not previously been considered by the PBAC.
- 5.6 No data were presented comparing nal-IRI with mFOLFOX6.
- 5.7 The resubmission claimed that 5-FU/folinic acid could be used as a proxy for mFOLFOX6. The PBAC previously acknowledged that 5-FU/folinic acid is not widely used in Australian practice, but in principle, it could be considered representative of the efficacy and toxicity of mFOLFOX6. However, due to limitations with the naïve indirect comparison provided in the previous submission (nal-IRI versus mFOLFOX6), the PBAC also acknowledged that confidence surrounding the relative efficacy between nal-IRI and oxaliplatin-containing regimens was necessarily low (paragraphs 7.4 and 7.6, irinotecan (nanoliposomal) PSD November 2016).
- 5.8 Details of the NAPOLI-1 trial are provided in the table below.

Table 3: Trial and associated reports presented in the resubmission

| Trial ID | Protocol title/ Publication title | Publication citation |
|----------|---|--|
| NAPOLI-1 | Wang-Gillam A et al (2016). Irinotecan (nanoliposomal) 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 |
| | Blanc J et al (2017). Subgroup analysis by prior non-liposomal irinotecan therapy in NAPOLI-1: a phase 3 study of nal-IRI±5-fluorouracil/leucovorin in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy | European Society for Medical Oncology 19 th World Congress on Gastrointestinal Cancer, Barcelona, Spain [poster only] |
| | 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 |
| | 90 day safety update report of the NAPOLI-1 study. The report contains 16 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 14 February 2014. [Date of analysis: 21 July 2015] | Internal study report |

Source: Table 2.2-1, pp39-40 and Attachment 1 of the resubmission

- 5.9 The key features of the NAPOLI-1 trial are summarised in the table below.

Table 4: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|--------------------------------------|-----|--|--------------|---|---|---|
| Nal-IRI vs. 5-FU/folinic acid | | | | | | |
| NAPOLI-1 | 236 | Multi-centre, randomised, open label trial 108 weeks + safety extension | High | Metastatic pancreatic cancer patients who have failed gemcitabine-based therapy | Overall survival, progression-free survival | Yes. Based on updated post-hoc analyses of irinotecan naïve subgroup and ITT population |

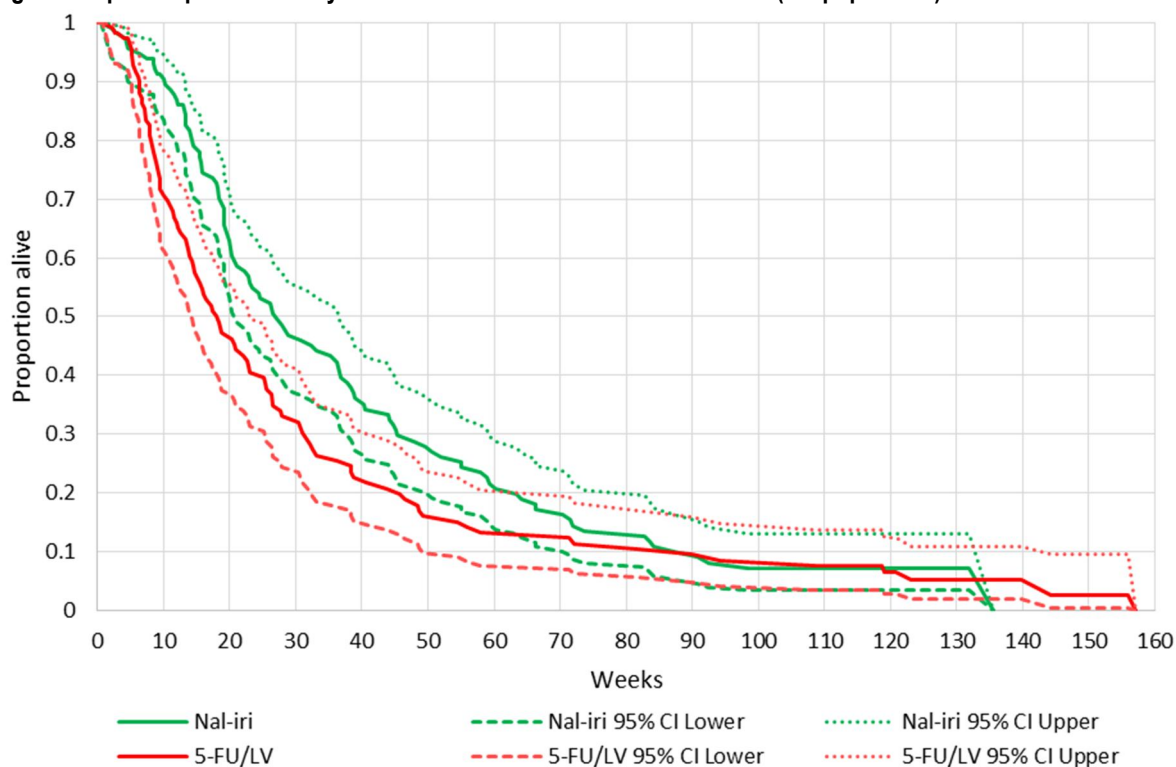
Source: Table 2.2-2, pp41-42 of the submission

- 5.10 The NAPOLI-1 trial had a high risk of bias due to the open-label design, particularly due to differences in frequency of monitoring (e.g. patients receiving nal-IRI had scheduled physical examinations every 2 weeks compared with patients allocated to 5-FU/folinic acid who were examined every 3 weeks) between treatment arms while patients remained on allocated treatments, leading to potential differences in disease management and detection bias between treatment arms.
- 5.11 Although outcome assessors were largely blinded, a limited number of personnel could be unblinded due to differences in visit schedules between treatment arms. There is typically a higher risk of bias for outcomes determined by investigators (e.g. progression-free survival) compared to objective outcomes such as overall survival.
- 5.12 There was potential for survivor bias due to differential discontinuations and follow-up between treatment arms in the NAPOLI-1 trial (more patients in the 5-FU/folinic acid arm did not receive treatment because of patient decision or withdrew consent for follow-up compared to the nal-IRI arm).
- 5.13 The PBAC noted that the submission did not present any evidence of comparative efficacy between irinotecan (nanoliposomal) and irinotecan.

Comparative effectiveness

- 5.14 The resubmission presented data for the NAPOLI-1 whole trial population and subgroups of patients with/without prior exposure to irinotecan.
- 5.15 The primary outcome of overall survival from the updated post-hoc analyses for the whole trial population from NAPOLI-1 is summarised in Figure 1 and Table 5 below.

Figure 1: Updated post-hoc analysis of overall survival from NAPOLI-1 trial (ITT population)



| Patients at risk | Weeks | | | | | | | |
|------------------|-------|-----|----|----|----|----|----|-----|
| | 0 | 10 | 20 | 30 | 40 | 55 | 71 | 108 |
| Nal-IRI | 117 | 104 | 71 | 52 | 40 | 28 | 18 | 8 |
| 5-FU/LV | 119 | 77 | 50 | 35 | 24 | 16 | 14 | 9 |

Source: 'KMOSPrior' Excel workbook and KM_OS_wk2_summary_Prot_v2_pats stata output, Appendix 4 of the resubmission
 Abbreviations: 5-FU/LV, 5-fluorouracil and folinic acid; CI, confidence interval; ITT, intent to treat; Nal-IRI, irinotecan (nanoliposomal) plus 5-FU/folinic acid

Table 5: Updated post-hoc analysis of overall survival from NAPOLI-1 (ITT population)

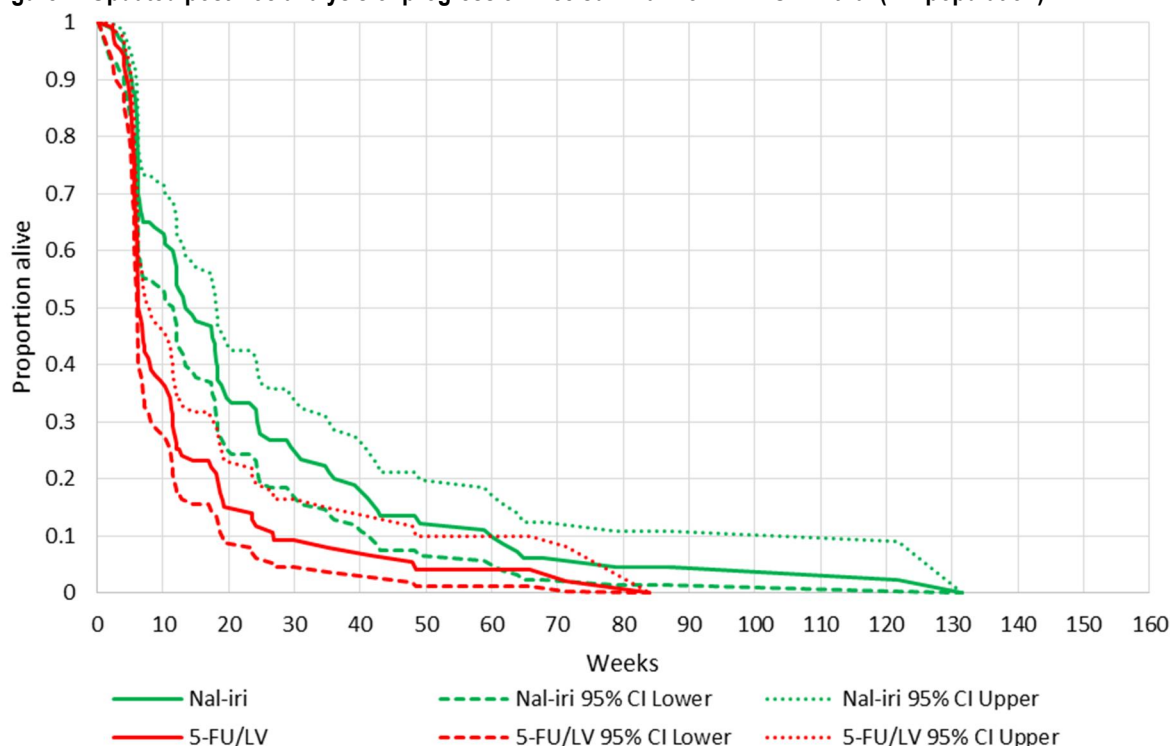
| Overall survival | Nal-IRI N=117 | 5-FU/folinic acid N=119 | HR (95% CI) |
|------------------------|-------------------|----------------------------|-------------------|
| Died, n/N (%) | 105/117 (89.7) | 102/119 (85.7) | 0.75 (0.57, 0.99) |
| Censored, n/N (%) | 12/117 (10.3) | 17/119 (14.3) | |
| Median, weeks (95% CI) | 27.1 (20.6, 36.6) | 18.4 (14.2, 23.1) | |

Source: Post Hoc Analyses, Appendix 4 of the resubmission
 Abbreviations: CI, confidence interval; HR, hazard ratio

5.16 Results from the updated post-hoc analysis show a statistically significant increase in median overall survival of 8.7 weeks associated with nal-IRI treatment compared with 5-FU/folinic acid (HR 0.75, 95% CI 0.57, 0.99). The survival curves converged between 80 and 90 weeks. The results were the same as the data presented in the previous submission (paragraph 6.15 irinotecan (nanoliposomal) PSD, November 2016).

5.17 Progression-free survival from the updated post-hoc analyses for the whole trial population from NAPOLI-1 is summarised in Figure 2 and Table 6 below.

Figure 2: Updated post-hoc analysis of progression-free survival from NAPOLI-1 trial (ITT population)



| Patients at risk | Weeks | | | | | | |
|------------------|-------|----|----|----|----|--------------------|--------------------|
| | 0 | 10 | 23 | 35 | 48 | 64/65 ^a | 83/87 ^a |
| Nal-IRI | 117 | 65 | 32 | 20 | 12 | 6 | 3 |
| 5-FU/LV | 119 | 38 | 13 | 7 | 4 | 3 | 1 |

Source: 'KMPFSPrior' Excel workbook, Appendix 4 of the resubmission

Abbreviations: 5-FU/LV, 5-fluorouracil and folinic acid; CI, confidence interval; ITT, intent to treat; Nal-IRI, irinotecan (nanoliposomal) plus 5-FU/folinic acid

^a No common timepoint for patients remaining at risk was available.

Table 6: Updated post-hoc analysis of progression-free survival from NAPOLI-1 (ITT population)

| Progression-free survival | Nal-IRI N=117 | 5-FU/folinic acid N=119 | HR (95% CI) |
|-------------------------------|-------------------|----------------------------|-------------------|
| Patients with events, n/N (%) | 95/117 (81.2) | 97/119 (81.5) | 0.57 (0.43, 0.76) |
| Censored, n/N (%) | 22/117 (18.8) | 22/119 (18.5) | |
| Median, weeks (95% CI) | 13.4 (11.7, 18.1) | 6.3 (6.1, 8.0) | |

Source: Post Hoc Analyses, Appendix 4 of the resubmission

Abbreviations: CI, confidence interval; HR, hazard ratio

5.18 Treatment with nal-IRI was associated with a statistically significant increase in median progression-free survival of 7.1 weeks compared with 5-FU/folinic acid (HR 0.57, 95% CI 0.43, 0.76). This was consistent with results in the previous submission, with only a small change in the median PFS for 5-FU/folinic acid as shown in the table below (paragraph 6.18, irinotecan (nanoliposomal) PSD, November 2016).

Table 7: Post-hoc analysis for progression-free survival (NAPOLI-1 trial) presented in the November 2016 submission

| Progression-free survival | Irinotecan (nanoliposomal) (N=117) | 5-FU/folinic acid (N=119) | HR (95%CI) |
|------------------------------|------------------------------------|---------------------------|-------------------------------|
| Patients with event, n/N (%) | 95/117 (81.2) | 97/119 (81.5) | 0.57 (0.43, 0.76) p=0.0001 |
| Progressed, n/N (%) | 76/117 (65.0) | 72/119 (60.5) | |
| Died, n/N (%) | 19/117 (16.2) | 25/119 (21.0) | |
| Median, weeks (95%CI) | 13.4 (11.7, 18.1) | 6.5 (6.1, 8.0) | |

Source: Table 14.2.2.1, Appendix 13 of the submission
Abbreviations: CI, confidence interval; HR, hazard ratio

5.19 Other secondary outcomes used included time to treatment failure, presented in the table below.

Table 8: Updated post-hoc analysis of time to treatment failure from NAPOLI-1 (ITT population)

| Time to treatment failure | Nal-IRI N=117 | 5-FU/folinic acid N=119 | HR (95% CI) |
|-------------------------------|---------------|-------------------------|-------------|
| Patients with events, n/N (%) | | | |
| Median, weeks (95% CI) | | | |

Source: Post Hoc Analyses, Appendix 4 of the resubmission
Abbreviations: CI, confidence interval; HR, hazard ratio

5.20 The results show a statistically significant increase in median time to treatment failure of [REDACTED] in patients receiving nal-IRI compared with 5-FU/folinic acid (HR [REDACTED], 95% CI [REDACTED]). This was consistent with results in the previous submission.

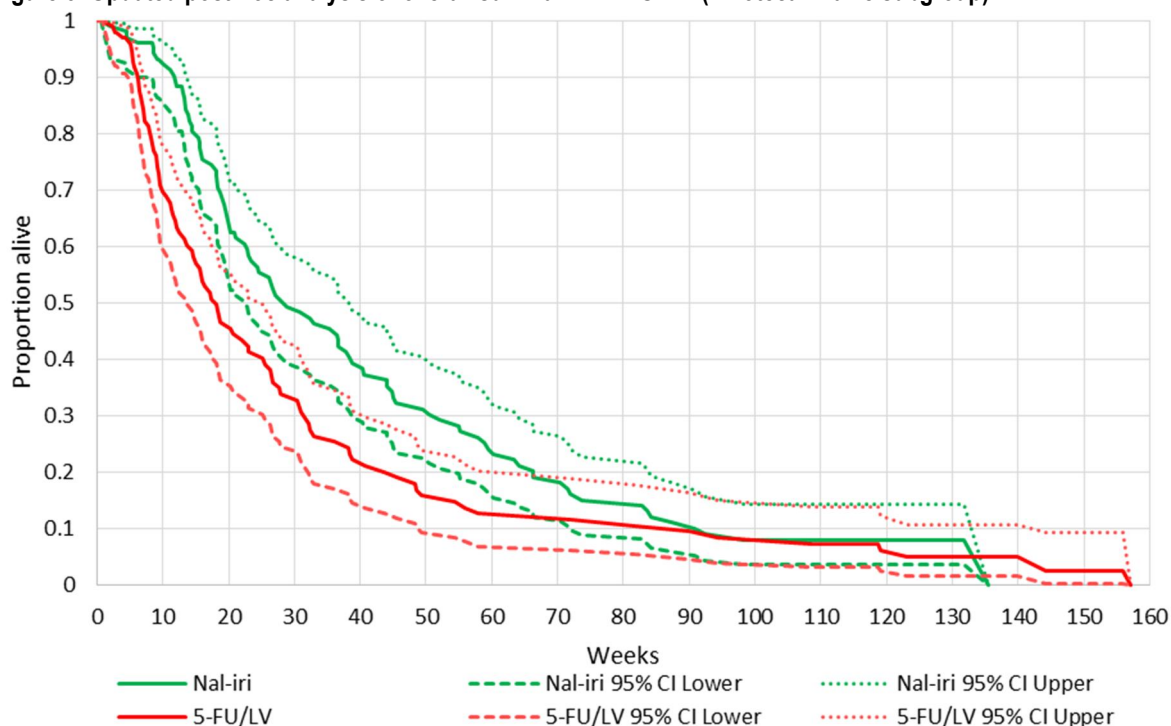
Subgroup analysis – prior irinotecan exposure

5.21 The resubmission presented additional post-hoc analyses for the subgroup of patients with no prior exposure to irinotecan and the complement of this subgroup (patients previously treated with irinotecan). However, the irinotecan experienced subgroup was a small sample size and there was substantial heterogeneity between treatment arms. A test for interaction based on the primary analysis period (data cut-off 14 February 2014) and the updated post-hoc analysis indicated that prior irinotecan exposure was not a treatment effect modifier. The ESC considered the post-hoc subgroup analyses based on prior irinotecan use to be uninformative given the limitations of the analyses noted above. Further, the ESC noted that the PSCR proposed the removal of the restriction criterion excluding patients with prior irinotecan exposure, and therefore considered that this subgroup analysis was no longer relevant to consideration of the submission.

5.22 There were no statistically significant differences in quality of life measures (EORTC-QLQ-C30, between nal-IRI and 5-FU/folinic acid. The resubmission stated that the results were of limited reliability due to poor data capture reflected in the high proportions of missing data at baseline.

5.23 The primary outcome of overall survival from the updated post-hoc analyses for the irinotecan naïve subgroup from NAPOLI-1 is summarised in Figure 3. Table 9 presents the results for overall survival in the irinotecan naïve and irinotecan experienced patients based on the updated post-hoc analyses from the NAPOLI-1 trial.

Figure 3: Updated post-hoc analysis of overall survival in NAPOLI-1 (irinotecan naïve subgroup)



| Patients at risk | Weeks | | | | | | | |
|------------------|-------|----|----|----|----|----|--------------------|-----|
| | 0 | 10 | 20 | 30 | 40 | 55 | 71/72 ^a | 108 |
| Nal-IRI | 105 | 95 | 65 | 49 | 39 | 28 | 18 | 8 |
| 5-FU/LV | 102 | 67 | 44 | 32 | 21 | 14 | 12 | 8 |

Source: 'KMOSPrior' Excel workbook, Appendix 4 of the resubmission

Abbreviations: 5-FU/LV, 5-fluorouracil and folinic acid; CI, confidence interval; Nal-IRI, irinotecan (nanoliposomal) plus 5-FU/folinic acid

^a No common timepoint for patients remaining at risk was available

Table 9: Updated post-hoc subgroup analysis of overall survival from NAPOLI-1

| Overall survival | Nal-IRI N=105 | 5-FU/folinic acid N=102 | HR (95% CI) |
|--|------------------|----------------------------|-------------|
| Irinotecan naïve subgroup | | | |
| Died, n/N (%) | | | ██████████ |
| Censored, n/N (%) | | | |
| Median, weeks (95% CI) | | | |
| Irinotecan experienced subgroup | | | |
| Died, n/N (%) | | | ██████████ |
| Censored, n/N (%) | | | |
| Median, weeks (95% CI) | | | |

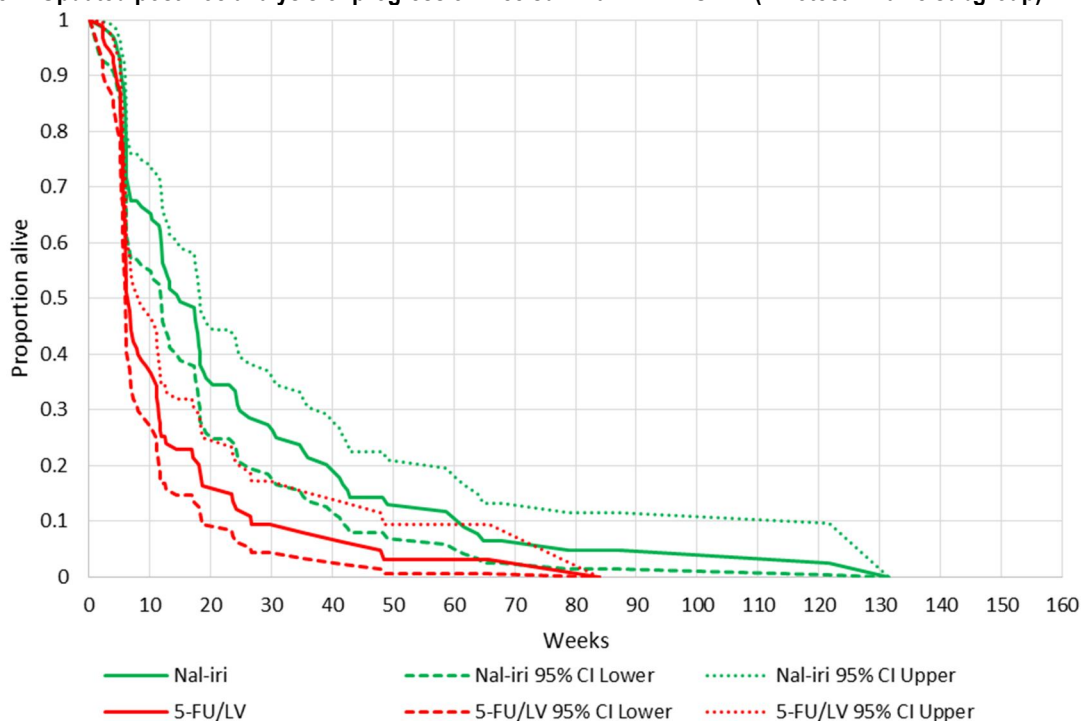
Source: Post Hoc Analyses, Appendix 4 of the resubmission

Abbreviations: CI, confidence interval; HR, hazard ratio

5.24 Treatment with nal-IRI was associated with a statistically significant increase in median overall survival of █████ weeks compared with 5-FU/folinic acid treatment in the irinotecan naïve patient subgroup (HR █████, 95% CI █████). The survival curves converge between 90 and 100 weeks. These results were numerically higher compared with an increase in median overall survival of 8.7 weeks associated with nal-IRI for the whole trial population (HR 0.75, 95% CI 0.57, 0.99).

5.25 Figure 4 presents the results for progression-free survival in irinotecan naïve patients. Table 10 presents the results for progression-free survival in the irinotecan naïve and irinotecan experienced patients based on the updated post-hoc analyses from the NAPOLI-1 trial.

Figure 4: Updated post-hoc analysis of progression-free survival in NAPOLI-1 (irinotecan naïve subgroup)



| Patients at risk | Weeks | | | | | | |
|------------------|-------|----|----|----|----|--------------------|--------------------|
| | 0 | 10 | 23 | 35 | 48 | 64/65 ^a | 83/87 ^a |
| Nal-IRI | 105 | 61 | 30 | 20 | 12 | 6 | 3 |
| 5-FU/LV | 102 | 34 | 12 | 6 | 3 | 2 | 1 |

Source: 'KMPFSPrior' Excel workbook, Appendix 4 of the resubmission

Abbreviations: 5-FU/LV, 5-fluorouracil and folinic acid; CI, confidence interval; ITT, intent to treat; Nal-IRI, irinotecan (nanoliposomal) plus 5-FU/folinic acid

^a No common timepoint for patients remaining at risk was available

Table 10: Updated post-hoc subgroup analysis of progression-free survival from NAPOLI-1

| Progression-free survival | Nal-IRI N=105 | 5-FU/folinic acid N=102 | HR (95% CI) |
|--|------------------|----------------------------|-------------|
| Irinotecan naïve subgroup | | | |
| Patients with events, n/N (%) | | | [Redacted] |
| Censored, n/N (%) | | | |
| Median, weeks (95% CI) | | | |
| Irinotecan experienced subgroup | | | |
| Patients with events, n/N (%) | | | [Redacted] |
| Censored, n/N (%) | | | |
| Median, weeks (95% CI) | | | |

Source: Post Hoc Analyses, Appendix 4 of the resubmission

Abbreviations: CI, confidence interval; HR, hazard ratio

- 5.26 There was a statistically significant increase in median progression-free survival of █ weeks associated with nal-IRI treatment compared with 5-FU/folinic acid in the subgroup of irinotecan naïve patients (HR █, 95% CI █). These results were numerically higher compared with an increased median progression-free survival of 7.1 weeks for the whole trial population (HR 0.57, 95% CI 0.43, 0.76).

Comparative harms

- 5.27 No comparative safety data were presented for nal-IRI and mFOLFOX6. The PSCR (p3) argued that the claim of non-inferior safety compared to mFOLFOX6 was made on the basis of PBAC's previous view that nal-IRI is likely to be of similar safety to oxaliplatin-containing regimens. The ESC noted that the PBAC had previously considered that 5 FU/folinic acid could be considered representative of the efficacy and toxicity of mFOLFOX6 (paragraph 6.38 irinotecan (nanoliposomal) November 2016 PSD).
- 5.28 The resubmission presented updated safety data for the whole trial population for selected severe treatment-related adverse events (grade 3 or more) based on post-hoc analyses of the NAPOLI-1 trial. These results appeared consistent with the safety data presented for the whole trial population in the November 2016 submission (paragraphs 6.25 and 6.27, irinotecan (nanoliposomal) PSD, November 2016).
- 5.29 Nal-IRI 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 nal-IRI compared with 5-FU/folinic acid that could substantially affect patients' quality of life such as diarrhoea, nausea, vomiting, fatigue, decreased appetite and neutropenia. The ESC considered that the observed treatment related adverse events in patients receiving nal-IRI would have a substantial impact on quality of life in patients where quality of life is likely to already be limited.
- 5.30 The trial also reported four treatment-related deaths in the irinotecan (nanoliposomal) monotherapy arm recorded as being due to five events (gastrointestinal toxicity, disseminated intravascular coagulation, pulmonary embolism, septic shock, enterocolitis infections).
- 5.31 The trial report noted higher use of supportive therapies such as granulocyte stimulating factors (G-CSF), blood transfusions and erythropoietin in patients receiving nal-IRI compared with 5-FU/folinic acid (e.g. █% versus █% of patients used G-CSF in the trial).
- 5.32 Based on the Periodic Safety Update Report (14 October 2016 to 13 April 2017) and 90-day safety update of the NAPOLI-1 trial provided in the expanded assessment of

harms, important identified risks associated with irinotecan (nanoliposomal) include diarrhoea, leukopenia/neutropenia, anaemia, acute infusion reactions and thromboembolic events. Important potential risks were identified as embryotoxicity/teratogenicity, hypersensitivity reactions, medication errors related to drug/dose confusion with non-liposomal irinotecan and interstitial lung disease. One event of fatal diarrhoea and one event of fatal neutropenic sepsis were reported in post-market safety data as possibly treatment-related.

- 5.33 The resubmission also presented new safety data for selected severe treatment-related adverse events (grade 3 or more) based on post-hoc analyses of the irinotecan naïve and complement subgroups. It was difficult to fully assess the comparative safety data for the subgroups due to the limited selection of data presented (no data presented for treatment-emergent adverse events of any severity, no data presented for serious treatment-related adverse events).
- 5.34 Based on the data presented, the safety profile for the irinotecan naïve subgroup (most common severe treatment-related adverse events) appeared similar to the safety data for the whole trial population. However, the safety profile for nal-IRI in irinotecan experienced patients remains uncertain given the low number of events from a relatively small number of patients (n=26). The ESC considered that given the irinotecan naïve subgroup captured the majority of patients in the trial, the safety signals were unlikely to differ from the whole trial population.

Benefits/harms

- 5.35 A summary of the comparative benefits and harms for nal-IRI versus 5-FU/folinic acid is presented in Table 11.

Table 11: Summary of comparative benefits and harms for nal-IRI and 5-FU/folinic acid (whole trial population)

| Benefits | Nal-IRI | 5-FU/folinic acid | Absolute Difference | HR (95% CI) |
|----------------------------------|----------------|--------------------------|----------------------------------|--------------------------|
| Overall survival | | | | |
| Died | 105/117 (89.7) | 102/119 (85.7) | 8.7 | 0.75 (0.57, 0.99) |
| Median OS (weeks) | 27.1 | 18.4 | | |
| Progression-free survival | | | | |
| Progressed or died | 95/117 (81.2) | 97/119 (81.5) | 7.1 | 0.57 (0.43, 0.76) |
| Median PFS (weeks) | 13.4 | 6.3 | | |
| Harms | Nal-IRI | 5-FU/folinic acid | Fatal or life-threatening | |
| | | | Nal-IRI | 5-FU/folinic acid |
| Diarrhoea | 72/117 (61.5) | 25/134 (18.7) | NR | NR |
| Nausea | 64/117 (54.7) | 40/134 (29.9) | NR | NR |
| Vomiting | 57/117 (48.7) | 27/134 (20.1) | NR | NR |
| Fatigue | 43/117 (36.8) | 27/134 (20.1) | NR | NR |
| Decreased appetite | 37/117 (31.6) | 16/134 (11.9) | NR | NR |
| Neutropenia/febrile neutropenia | 36/117 (30.8) | 3/134 (2.2) | NR | NR |
| Anaemia | 20/117 (17.1) | 16/134 (11.9) | NR | NR |
| Treatment-related death | - | - | 1/117 (0.9) | 0/134 (0) |

Source: Post Hoc Analyses, Appendix 4 and p80 of the resubmission

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

- 5.36 On the basis of the direct evidence presented in the resubmission, treatment with nal-IRI compared with 5-FU/folinic acid results in a statistically significant increase in overall survival (median of approximately 9 weeks) and progression-free survival (median of approximately 7 weeks) in the whole trial population.
- 5.37 On the basis of the direct evidence presented by the resubmission, for every 100 patients treated with nal-IRI compared with 5-FU/folinic acid over a follow-up period of at least 25 months, approximately:
- 43 additional patients would have treatment-related diarrhoea
 - 25 additional patients would have treatment-related nausea
 - 29 additional patients would have treatment-related vomiting
 - 17 additional patients would have treatment-related fatigue
 - 20 additional patients would have treatment-related decreased appetite
 - 29 additional patients would have treatment-related neutropenia
 - 5 additional patients would have treatment-related anaemia
 - 1 additional patient would experience treatment-related death

Clinical claim

- 5.38 The resubmission described nal-IRI as superior in terms of efficacy compared to mFOLFOX6 (using 5-FU/folinic acid monotherapy as a proxy). The PBAC considered that the inherent uncertainty introduced by using a proxy to demonstrate comparative efficacy made it difficult to ascertain if the claim of superior efficacy was reasonable.
- 5.39 The ESC noted that the approach used in the resubmission (using 5-FU/folinic acid as a proxy) assumes that the oxaliplatin component in the mFOLFOX6 regimen provides no additional benefit. The ESC noted that no information provided in the submission supported the assumption that the oxaliplatin component in mFOLFOX6 does not provide additional benefit. The ESC also noted that the incremental benefit of nal-IRI over 5-FU/folinic acid observed in the NAPOLI-1 trial (9 weeks gain in overall survival) was previously considered by the PBAC to be the upper limit of a plausible incremental benefit over oxaliplatin-containing regimens. Further, the PBAC noted that no evidence had been presented to support a claim that nanoliposomal irinotecan would confer any additional benefit over the non-nanoliposomal irinotecan currently available for use in this setting (FOLFIRI).
- 5.40 The resubmission described nal-IRI as non-inferior in terms of safety compared to mFOLFOX6 (using 5-FU/folinic acid monotherapy as a proxy). No data were presented in the resubmission comparing the safety of nal-IRI versus mFOLFOX6. In terms of safety, the PBAC previously considered that nal-IRI is likely to be of similar safety compared to oxaliplatin-containing regimens (with both regimens having significant toxicities) but may be inferior to some other alternative second-line treatment options, such as capecitabine monotherapy. The ESC noted the significantly higher incidence of treatment related AEs and higher number of

patients treated with nal-IRI who had at least one dose reduction compared with those treated with 5-FU/folinic acid. The ESC therefore considered that the claim of non-inferior safety was not supported by the evidence presented.

- 5.41 The PBAC maintained that irinotecan (nanoliposomal) is likely to be of similar safety to oxaliplatin-containing regimens (with both regimens having significant toxicities) and therefore considered the claim of non-inferior safety compared to mFOLFOX6 to be acceptable.

Economic analysis

- 5.42 The PBAC considered that on the basis that superior comparative efficacy had not been accepted, that a cost-minimisation analysis may be more appropriate.
- 5.43 The resubmission presented two separate trial-based cost-effectiveness analyses comparing nal-IRI with mFOLFOX6 (using 5-FU/folinic acid as a proxy) based on the whole trial population with metastatic pancreatic adenocarcinoma who previously failed gemcitabine-based therapy and the subgroup of irinotecan naïve patients. The ESC considered that the analysis based on the whole trial population was appropriate for determining the cost-effectiveness of nal-IRI for the treatment of metastatic pancreatic adenocarcinoma for patients who previously failed gemcitabine-based therapy. The ESC did not consider the economic analysis presented for the irinotecan naïve subgroup to be reliable given the limitations of the post-hoc analyses for this subgroup. Further, the ESC noted that the PSCR proposed removal of the restriction criterion that patients be irinotecan naïve, and therefore the analysis based on this subgroup would no longer be relevant to the submission.
- 5.44 The PBAC previously considered a trial-based analysis was more appropriate given the maturity of the clinical data where the majority of events were captured before the end of the trial. The PBAC recommended that a resubmission should present a comparison of nal-IRI with mFOLFOX6, using the trial results compared with 5-FU/folinic acid from the NAPOLI-1 trial as a proxy for the incremental benefit over oxaliplatin-containing regimens.
- 5.45 Table 12 summarises the key components of the model compared to the November 2016 submission.

Table 12: Key components of the economic evaluation

| Component | Summary |
|----------------------------------|---|
| Time horizon | 3 years (versus 5 years for the November 2016 submission) |
| Outcomes | Life years (versus quality adjusted life years in the November 2016 submission) |
| Methods used to generate results | Partitioned survival analysis (same as for November 2016 submission) |
| Health states | Pre-progression on-treatment, pre-progression off-treatment, post-progression, death (same as for November 2016 submission) |
| Cycle length | 1 week; half-cycle correction applied to both outcomes and costs (same as for November 2016 submission) |
| Methods used to generate results | Kaplan-Meier curves for overall survival, progression-free survival and time to treatment failure based on NAPOLI-1 trial population and irinotecan naïve subgroup (trial data with longer follow-up and subgroup data included in the model versus the November 2016 submission) |

Source: Table 3.1-1, p102 of the resubmission

5.46 The key differences between the November 2016 submission and the resubmission are:

- removal of utility estimates in the resubmission, with outcomes based on life year gained only;
- trial-based economic analysis with no modelled extrapolation over 3 years versus a modelled analysis over 5 years previously;
- new clinical data based on updated post-hoc analyses from the NAPOLI-1 trial for the irinotecan naïve subgroup and ITT population (numerical increase in survival benefit in the irinotecan naïve subgroup compared to whole trial population);
- decreased drug cost associated with nal-IRI primarily due to the change in approach used to calculate cost of the irinotecan (nanoliposomal) component (based on a fixed-vial distribution);
- increased drug cost associated with mFOLFOX6 largely due to change in dosing regimen used to estimate drug costs (trial instead of guidelines-based);
- decreased adverse event costs primarily due to the included distribution between hospital and non-hospital costs; and
- decreased post-progression treatment costs assuming patients received FOLFIRINOX as post-progression treatment.

5.47 Key drivers of the economic model in the resubmission are summarised in the following table.

Table 13: Key drivers of the model

| Description | Method/Value | Impact |
|-------------------------------------|---|---------------------------|
| Survival benefit | Based on updated post-hoc analyses of NAPOLI-1 trial population and irinotecan naïve subgroup (3 years including follow-up). It was unclear whether the incremental survival benefit from the trial could be directly applied in the model given the magnitude of incremental benefit versus mFOLFOX6 remained uncertain. A mean difference in overall survival of 8.0 weeks was estimated from the economic model for the ITT population for the whole follow-up period. The mean difference in overall survival to the point at which the nal-IRI and 5FU/folinic acid curves converge in the KM data was approximately 8.7 weeks, which is longer than estimated by the model. | Unclear |
| Treatment costs | The revised treatment costs associated with nal-IRI are substantially lower whereas treatment costs for mFOLFOX6 have increased compared to the November 2016 submission. The estimates were highly uncertain due to the following issues: <ul style="list-style-type: none"> • There are a wide range of treatment regimens in addition to mFOLFOX6 that are likely to be substituted which are less expensive (such as capecitabine and XELOX) than the mFOLFOX6 regimen. The model was sensitive to alternative comparator treatment costs. • The resubmission applied the trial-based dosing regimen for mFOLFOX6 that uses a higher dose of folinic acid (400 mg/m²) than recommended in guidelines (50 mg). This resulted in a higher cost compared to the previous submission that used doses as recommended in guidelines. | High, favours nal-IRI |
| Post-progression treatment duration | The model inappropriately assumed that the proportion of patients in the nal-IRI (31%) and 5-FU/folinic acid (38%) arms that received post-progression treatments were treated continuously until death. | Moderate, favours nal-IRI |
| Adverse event costs | The revised adverse event costs associated with nal-IRI and mFOLFOX6 were lower compared to the November 2016 submission. The cost of managing adverse events may not be reliable estimates due to a likely underestimation of hospitalised events, drug costs for acute events were based on proportion used instead of full prescription costs, and estimated costs did not account for the increased use of supportive therapies not directly related to an adverse event (e.g. granulocyte growth factor or blood transfusions). | Moderate, favours nal-IRI |
| Quality adjusted life years | Utility values were not incorporated in the economic analyses. | High, favours nal-IRI |

Source: compiled during the evaluation

Abbreviations: BSA, body surface area; ITT, intent to treat; nal-IRI, irinotecan (nanoliposomal) plus 5-FU/folinic acid; OS, overall survival

5.48 The ESC considered that although different from the previous submission, given the economic model in this resubmission was trial based, the approach to estimate the cost of nal-IRI was appropriate. The ESC noted that the average number of vials per 2-week cycle used in the model was based on the number of vials administered per patient in the NAPOLI-1 trial.

5.49 The November 2016 submission presented an incremental cost per life year gained of \$75,000 - \$105,000 when comparing nal-IRI with mFOLFOX6. The corresponding incremental cost per QALY gained presented was \$105,000 – \$200,000. In consideration of the November 2016 resubmission, the PBAC considered that a revised base case ICER should not exceed \$50,000 per QALY gained.

- 5.50 The resubmission presented results based on an incremental cost per life year gained, stating that the NAPOLI-1 trial did not collect utility values and the PBAC considered that the utility values used in the previous submission for pre-progression (0.8) and post-progression (0.75) were inappropriately high for patients with metastatic pancreatic cancer (paragraph 7.8 irinotecan (nanoliposomal) November 2016 PSD).
- 5.51 The resubmission also stated that this approach was considered by the PBAC when evaluating the nab-paclitaxel March 2014 submission for the treatment of locally advanced, unresectable or metastatic pancreatic adenocarcinoma. “The PBAC considered that at an ICER of between \$45,000 to \$75,000 per life year gained, nab-paclitaxel would not be cost-effective. The PBAC considered that the cost-effectiveness of nab-paclitaxel would be acceptable at an ICER of between \$50,000 to \$90,000 per QALY gained, which would be comparable with that of other recent medicines where there is high unmet clinical need. The PBAC considered that an ICER in the range of \$15,000 to \$45,000 per life year gained would be appropriate to account for the lack of adjustment of quality of life” (nab-paclitaxel March 2014 PSD).
- 5.52 The results of the economic evaluation are summarised in the table below.

Table 14: Results of the economic evaluation (ITT)

| Component | Nal-IRI | mFOLFOX6 | Increment |
|--|---------------|---------------|---------------|
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Life years | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost per life year gained | | | \$ [REDACTED] |

Source: Table 3.8-1, p142 and Table 3.9-1, p145 of the resubmission

- 5.53 In the ITT population, treatment with nal-IRI was associated with an incremental cost (ICER) per life year (LY) gained of \$75,000 - \$105,000 compared to mFOLFOX6 (using 5-FU/folinic acid as a proxy). For the irinotecan naïve subgroup, the ICER/LY gained was \$45,000 - \$75,000. The ESC noted that the revised base case presented in the PSCR resulted in an ICER per LY gained of \$75,000 - \$105,000.
- 5.54 The PSCR presented revised economic analyses for the ITT and irinotecan naïve subgroup (see Table 15 below for the ITT results). The ESC noted that the following changes were made in the respecified base case analyses:
- Hospitalisation assumed for all adverse events. This increased the weekly adverse event cost of nal-IRI to \$229.03 from \$25.03, and for mFOLFOX6 to \$50.80 from \$6.24. The ICER increased to \$75,000-\$105,000 per LY gained (from \$75,000-\$105,000).
 - Same adverse event rates and associated weekly costs assumed for the nal-IRI and mFOLFOX6 arms. This reduced the ICER to \$75,000-\$105,000 per LY gained (from \$75,000-\$105,000). The ESC considered that this change to the

model inputs may not be acceptable in the context of the claim of non-inferior safety being unsupported.

- Weekly administration cost associated with post-progression treatment FOLFIRINOX reduced to \$81.60 from \$130.58. This resulted in administration cost for FOLFIRINOX being the same as for mFOLFOX6 and nal-IRI. The ICER increased slightly to \$75,000-\$105,000 per LY gained (from \$75,000 - \$105,000), which was presented as the revised base case.

5.55 The ESC noted that the PSCR did not provide sufficient justification for the assumption of equal adverse event rates in the nal-IRI and mFOLFOX6 arms. Other issues raised during the evaluation remain, including the post-progression treatment duration and the fact that mFOLFOX6 is the most expensive of the range of treatment options that could be replaced by nal-IRI. The PBAC noted that there were higher rates of GCSF use in the nal-IRI arm, and that the costs of this had not been included in the model.

Table 15: Results of the revised economic evaluation (ITT)

| Component | Nal-IRI | mFOLFOX6 | Increment |
|--|---------------|---------------|----------------------|
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Life years | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost per life year gained | | | \$ [REDACTED] |

Source: Table 1, p1 of the PSCR

5.56 Although the use of incremental cost per life year gained may be reasonable, the result does not capture the impact of this disease on quality of life which is likely to be substantial in this particular setting (poor prognosis, treatments associated with considerable toxicities). The ESC noted that the updated literature search for published utility studies presented in the submission indicated that the utility value for pancreatic patients may be as low as 0.6. As such, the ESC considered that the incremental cost per QALY gained would likely be substantially higher than the incremental cost per life year gained and the ICER the PBAC previously considered would be cost-effective for nab-paclitaxel. The PBAC considered that the approach of using LY instead of QALYs was inappropriate.

5.57 The results of key sensitivity analyses are summarised below. These were based on the original base case provided with the resubmission, not the revised base case provided in the PSCR.

Table 16: Results of key sensitivity analyses

| | Incremental cost | Incremental LY | ICER |
|---|--|--|--|
| Univariate analyses | | | |
| Base case (irinotecan naïve subgroup) | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] |
| Comparator (changing drug costs only) ^a Capecitabine monotherapy \$28.70/week Capecitabine monotherapy \$46.82/week XELOX (capecitabine plus oxaliplatin) \$72.06/week | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] |
| Using same approach to costing irinotecan (nanoliposomal) as other drugs (efficient vial combination 3x43 mg per cycle; \$ [REDACTED]) applied to proportion on treatment | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] |
| Alternative distributions for hospital vs. non-hospital costs for severe treatment-related adverse events 25% hospitalised 50% hospitalised 75% hospitalised 100% hospitalised | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] |
| ITT population survival benefit | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] |
| Comparator (changing drug costs only) ^a Capecitabine monotherapy \$29.33/week Capecitabine monotherapy \$47.86/week XELOX (capecitabine plus oxaliplatin) \$72.57/week | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] |
| Using same approach to costing irinotecan (nanoliposomal) as other drugs (efficient vial combination 3x43mg per cycle; \$ [REDACTED]) applied to proportion on treatment | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] |
| Alternative distributions for hospital vs. non-hospital costs for severe treatment-related adverse events - 25% hospitalised - 50% hospitalised - 75% hospitalised - 100% hospitalised | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] |
| Multivariate analyses | | | |
| ITT population survival benefit, using same approach to costing irinotecan (nanoliposomal) as other drugs (efficient vial combination 3x43mg per cycle; \$ [REDACTED]) applied to proportion on treatment and adjusting comparator costs ^a Capecitabine monotherapy \$29.33/week Capecitabine monotherapy \$47.86/week XELOX (capecitabine plus oxaliplatin) \$72.57/week | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] |

Source: compiled during the evaluation using 'ONIVYDE (nanoliposomal irinotecan) Economic Evaluation – Base Case' and 'ONIVYDE (nanoliposomal irinotecan) Economic Evaluation – ITT population' Excel workbooks of the resubmission

^a Based on trial-based dosing regimens from Boeck 2008 and Cartwright 2002 publications

5.58 The sensitivity analyses indicated that the economic model was sensitive to the approach used to estimate the irinotecan (nanoliposomal) drug cost, the use of alternative distributions of hospitalised versus non-hospitalised adverse event costs and alternative comparator treatment costs.

5.59 Sensitivity analyses based on an estimated cost of \$ [REDACTED] for irinotecan (nanoliposomal) per treatment cycle (estimated total cost of nal-IRI of \$ [REDACTED]) and estimated comparator costs based on capecitabine monotherapy or XELOX resulted in incremental costs per life year gained of \$105,000-\$200,000.

- 5.60 The pre-PBAC response proposed a revised risk sharing arrangement (RSA) which may reduce the average cost of irinotecan (nanoliposomal), and therefore the ICER. The sponsor proposed to provide an additional rebate of [REDACTED] % of the effective price for all utilisation above [REDACTED] % of the expected expenditure. The pre-PBAC response claimed that if utilisation was as expected, the risk sharing arrangement would effectively reduce the ICER to \$45,000-\$75,000 per LYG for the ITT population. The PBAC noted that this ICER was based on the model presented in the resubmission with a base case of \$75,000-\$105,000 per LYG rather than the respecified base case presented in the PSCR with an ICER of \$75,000-\$105,000 per LYG, which was unjustified. The PBAC noted that applying the revised base case to the proposed approach, the ICER increased to \$45,000-\$75,000 per LYG. The PBAC noted that the ICER would only be achieved if utilisation was as estimated. For assessments of cost-effectiveness to rely on RSA rebates, the PBAC advised that it would need to have a high level of confidence in the utilisation estimates underpinning the RSA. Given the remaining concerns regarding the estimation of the eligible patient population and uptake rates, the PBAC considered that there was substantial uncertainty in the financial estimates that had been provided.
- 5.61 The PBAC noted the average price for irinotecan (nanoliposomal) and hence the ICER would depend on the extent of use and this further increased the uncertainty associated with the ICER, especially given the utilisation and financial estimates on which the rebate caps are based are uncertain.

Drug cost/patient/cycle

- 5.62 The drug cost per patient per cycle (2 weeks) for nal-IRI in combination with 5-FU/folinic acid was approximately \$[REDACTED] (Section 100, Efficient Funding of Chemotherapy dispensed price). This was calculated using the proposed effective dispensed price and trial-based body surface area of 1.73 m² and [REDACTED] % dose intensity, requiring [REDACTED] mg of irinotecan (nanoliposomal) (3 vials), 3,176 mg of 5-FU (1 x 500 mg and 3 x 1000 mg vials) and 529 mg of folinic acid (average cost of \$0.08 per mg). The resubmission assumed that 31% of the drug would be dispensed in public hospitals and 69% in private hospitals.
- 5.63 The drug cost per patient per cycle (2 weeks) for mFOLFOX6 was approximately \$424 based on the same body surface area and dose intensity, requiring 112 mg of oxaliplatin (1 x 50 mg and 1 x 100 mg vial), 3,705 mg of 5-FU (1 x 500 mg and 3 x 1000 mg vials) and 529 mg of folinic acid (average cost of \$0.08 per mg). This cost was higher than used in the previous submission (\$339), primarily due to the use of a higher, trial-based, dose of 400 mg/m² for folinic acid whereas the previous submission more appropriately used the 50 mg bolus dose as recommended in guidelines. The PBAC agreed with the ESC that it would have been more appropriate to use the 50 mg bolus dose as per recommended guidelines as this is the likely dose to be used in clinical practice.

5.64 The drug costs per patient per course were estimated to be \$ [REDACTED] for nal-IRI and \$2,118 for mFOLFOX6, based on the modelled treatment durations for nal-IRI and mFOLFOX6 used in the ITT economic model (approximately [REDACTED] weeks and [REDACTED] weeks, respectively).

Estimated PBS usage & financial implications

5.65 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation/financial implications associated with the PBS listing of irinotecan (nanoliposomal) over the first 6 years of listing.

Table 17: Estimated use and financial implications

| | Year 1 (2018) | Year 2 (2019) | Year 3 (2020) | Year 4 (2021) | Year 5 (2022) | Year 6 (2023) |
|---|------------------|------------------|------------------|------------------|------------------|------------------|
| Incident pancreatic cancer patients | 3,335 | 3,434 | 3,534 | 3,636 | 3,738 | 3,842 |
| Patients using 2 nd line palliative chemotherapy | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Patients using 3 rd line palliative chemotherapy | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Total patients treated with nal-IRI | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Effective cost of irinotecan (nanoliposomal) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Cost of concomitant 5-FU | \$816,314 | \$1,082,969 | \$1,218,518 | \$1,291,907 | \$1,363,519 | \$1,419,439 |
| Cost of concomitant folinic acid | \$268,314 | \$355,961 | \$400,515 | \$424,637 | \$448,175 | \$466,555 |
| Drug costs to manage adverse events | \$32,351 | \$42,918 | \$48,291 | \$51,198 | \$54,036 | \$56,253 |
| Total cost of treatment with nal-IRI | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Patient co-payments | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] |
| Cost of substituted mFOLFOX6 regimen | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] | -\$ [REDACTED] |
| Net cost to PBS/RPBS | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Incremental MBS costs for treatment administration, adverse events and monitoring | \$948,554 | \$1,258,407 | \$1,415,915 | \$1,501,193 | \$1,584,405 | \$1,649,385 |
| Total cost to government | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |

Source: Table 4.1-7, p156; Table 4.1-8, p157; Table 4.1-11, pp159-160; Table 4.1-12, p160; Table 4.1-14, pp161-162; Table 4.1-19, p165; Table 4.1-20, p166; Table 4.1-22, p167; Table 4.1-23, p168; Table 4.1-24, p168; Table 4.1-25, p169; Table 4.1-26, p169 of the resubmission

Abbreviations: MBS, Medicare Benefits Schedule; nal-IRI, irinotecan (nanoliposomal) plus 5-FU/folinic acid; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

5.66 The resubmission estimated that in Year 1, the number of patients treated would be less than 10,000 at a net cost to the PBS of less than \$10 million, increasing to less than 10,000 patients in Year 6 at a net cost to the PBS of \$10-\$20 million (compared with [REDACTED] patients and \$ [REDACTED] in Year 1, increasing to [REDACTED] patients and \$ [REDACTED] million in Year 5 based on the PSCR for the November 2016 submission. The

difference in patient numbers was primarily due to the inclusion of non-metastatic patients with no attempted resection in the current estimates who were previously excluded in the November 2016 estimates. This was consistent with DUSC advice (irinotecan (nanoliposomal) DUSC advice November 2016).

5.67 The estimated utilisation and financial implications were highly uncertain due to the following issues:

- The size of the eligible patient population was uncertain due to unsupported assumptions regarding treatment rates in different lines of therapy, not including patients who qualify for treatment with nal-IRI from having prior non-metastatic treatment and inadequate accounting of patients who experience disease recurrence after 12 months. These issues were previously raised by DUSC and were inadequately addressed in the resubmission. The estimated patient numbers may be substantial under or over estimates;
- Uptake rates were based on unsupported assumptions with no justification of patterns in second-line and third-line therapy
 - DUSC has previously noted the poor side effect profile associated with nal-IRI which may affect its uptake in real-world palliative care populations (which are likely to include more patients with poorer performance status than trial populations) (irinotecan (nanoliposomal) DUSC advice November 2016);
 - DUSC has previously noted the poor outcomes associated with treatment for pancreatic cancer (including nal-IRI) and suggested that patients with good performance status will trial multiple regimens and the market will be highly sensitive to the availability of new treatments in the future (irinotecan (nanoliposomal) DUSC advice November 2016).
- Drug costs, administration costs, adverse event costs and monitoring costs have been imported from the economic evaluation and therefore incorporate all the issues of concern with these estimates (such as underestimation of irinotecan (nanoliposomal) costs, underestimation of adverse event costs, and uncertainty in the subsequent-line therapy costs). Additionally, multi-year costs from the economic evaluation are attributed to single years in the budget impact model. This issue was previously raised by DUSC and was not addressed in the resubmission (irinotecan (nanoliposomal) DUSC advice November 2016);
- The resubmission assumed that the mFOLFOX6 drug regimen could act as a proxy for all drug regimens potentially substituted by nal-IRI. There is likely to be substantial variation in overall costs between individual regimens (e.g. capecitabine monotherapy versus FOLFIRINOX) and substituted therapies which represent a major cost-offset in the budget impact model. DUSC previously raised this assumption as a concern which was not addressed in the resubmission (irinotecan (nanoliposomal) DUSC advice November 2016).

Quality Use of Medicines

- 5.68 No quality use of medicines issues were identified in the resubmission. However, there are potential issues for consideration that were identified during the evaluation:
- There is potential for administration of the incorrect drug as well as the incorrect dose due to the availability of other formulations and strengths of irinotecan (non-liposomal irinotecan). This issue has been identified in the Periodic Safety Update Report (14 October 2016 to 13 April 2017) and included as a black box warning in the product information.
 - All patients in the NAPOLI-1 trial underwent UGT1A1 genotype testing and those who were homozygous for the UGT1A1*28 allele received a reduced initial dose of irinotecan (nanoliposomal) due to increased risk of neutropenia. This was consistent with dosing recommendations in the product information. While UGT1A1 genotype testing is available in Australia, it is not rebated and therefore these patients may not be identified in practice.

Financial Management – Risk Sharing Arrangements

- 5.69 The PSCR acknowledged the uncertainties with the financial estimates and proposed a risk sharing arrangement to manage this. However, no details of the proposed risk sharing arrangement were provided.
- 5.70 The pre-PBAC Response proposed that the risk sharing arrangement take the form of a rebate of ■■■% above expenditure with expenditure caps set to ■■■% of the predicted total Commonwealth expenditure.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC did not recommend the listing of irinotecan (in the form of I.V. injection containing nanoliposomal 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. The PBAC based its decision on unacceptably high incremental cost-effectiveness in the context of a modest and uncertain incremental clinical benefit.
- 6.2 The PBAC reaffirmed 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. The PBAC noted the consumer comments received relating to this submission, including from the Medical Oncology Group of Australia (MOGA). The PBAC noted that MOGA expressed support for the irinotecan (nanoliposomal) submission, and based on the European Society for Medical

Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) the rating was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).

- 6.3 The PBAC noted that as per the November 2016 major submission, the resubmission's proposed clinical place for nal-IRI was as an alternative treatment in patients with metastatic pancreatic adenocarcinoma who have progressed after previous treatment with gemcitabine-based therapy. The PBAC noted that the submission did not provide evidence to support PBS-subsidised use of irinotecan (nanoliposomal) as a replacement for irinotecan in irinotecan-containing therapies in the same line of treatment, such as FOLFIRINOX.
- 6.4 The PBAC considered the submission's nominated comparator of mFOLFOX6 was reasonable. The PBAC recalled it previously considered that the most relevant comparators are oxaliplatin-containing regimens such as mFOLFOX6, and capecitabine. The PBAC considered that alternative therapies used following gemcitabine-based therapy (e.g. FOLFIRINOX, FOLFIRI, XELOX, capecitabine) could also be considered alternative comparators.
- 6.5 The PBAC noted that as per the November 2016 major submission, the resubmission was based on one head-to-head, open label trial comparing irinotecan (nanoliposomal) with 5-FU/folinic acid: NAPOLI-1 (n=236). The PBAC noted that the resubmission presented new *post-hoc* analyses based on data with additional follow-up (follow-up period not reported) from the NAPOLI-1 trial. The results for these analyses (increase in median OS of 8.7 weeks; increase in median PFS of 7.1 weeks) were similar to those reported in the November 2016 submission.
- 6.6 The PBAC considered while the evidence presented supported a superior benefit of treatment with nal-IRI compared with 5-FU/folinic acid, the submission's claim of superior efficacy compared with mFOLFOX6 (using 5-FU/folinic acid as a proxy) was uncertain. While the PBAC recalled it previously considered that in principle, 5-FU/folinic acid could be considered representative of the efficacy and toxicity of mFOLFOX6, the inherent uncertainty associated with using a proxy in an analysis of comparative efficacy meant that there was low confidence regarding the extent of benefit. The PBAC noted that the approach of using 5-FU/folinic acid as a proxy implicitly assumes the oxaliplatin component in the mFOLFOX6 regimen provides no additional benefit, and this was not supported. The PBAC considered that by extension, the claim of superior efficacy of nal-IRI over other combination therapies in the second line treatment setting was uncertain. Further, the PBAC considered there was no evidence to support the use of irinotecan (nanoliposomal) as an alternative to non nanoliposomal irinotecan within combination therapies.
- 6.7 The PBAC considered that nal-IRI is inferior in terms of safety compared to 5-FU/folinic acid noting that nal-IRI was associated with significantly higher incidences of treatment-related adverse events and a higher rate of dose reduction compared with 5-FU/folinic acid. The PBAC considered that nal-IRI is likely to be of similar

safety to mFOLFOX6 and other oxaliplatin-containing regimens.

- 6.8 The PBAC noted that the resubmission presented a trial-based analysis comparing nal-IRI to mFOLFOX6 (using 5-FU/folinic acid as a proxy for efficacy) which estimated the incremental cost per life-year gained (LYG). The PBAC noted that the revised base case presented in the PSCR, which incorporated a number of changes (see paragraph 5.51), resulted in an increase in the cost per LYG to \$75,000-\$105,000 from \$75,000-\$105,000. The PBAC noted that the revised base case addressed some uncertainties in the model relating to the proportion of adverse events resulting in hospitalisation and the difference in weekly post-progression administration costs applied to each arm. However, the PBAC noted that the revised base case did not address all outstanding issues (see paragraph 5.55) and therefore considered that the revised based case remained uncertain.
- 6.9 The PBAC noted the ICER was sensitive to alternative comparator treatment costs; the ICER increased to \$75,000-\$105,000 per LYG when alternative comparator costs were applied. Further, the PBAC considered it appropriate to incorporate quality of life in the analysis and report the results using QALYs gained given the impact of the disease and treatment on quality of life is likely to be substantial. The PBAC agreed with the ESC that the incremental cost per QALY gained would likely be substantially higher than the incremental cost per LYG presented. Accordingly, the PBAC considered that the ICER was likely to be substantially higher than that previously advised of less than \$50,000 per QALY gained.
- 6.10 The PBAC noted that several issues previously raised by the DUSC regarding the estimation of the eligible patient population and uptake rates had not been addressed in the resubmission (see paragraph 5.66) and therefore considered that the estimated financial implications remained uncertain.
- 6.11 The PBAC noted that in their pre-PBAC response , the sponsor proposed a rebate set at a threshold of ■% of predicted Commonwealth expenditure, and this was estimated to reduce the ICER to \$45,000-\$75,000 per LYG. Given the clinical and modelling issues noted above, the PBAC considered the estimated ICER to be uncertain and incorporating a reduction in the irinotecan (nanoliposomal) price based on the proposed RSA further increased the uncertainty. Further, the PBAC noted that the ICER would only be achieved if utilisation was as estimated. For assessments of cost-effectiveness to rely on RSA rebates, the PBAC advised that it would need to have a high level of confidence in the utilisation estimates underpinning the RSA. Given the remaining concerns regarding the estimation of the eligible patient population and uptake rates, the PBAC considered that there was substantial uncertainty in the financial estimates that had been provided.
- 6.12 Given the modest clinical benefit of nal-IRI over 5-FU/folinic acid, and the highly uncertain extent of benefit of nal-IRI over mFOLFOX6 and other regimens used following gemcitabine-based therapy, the PBAC recommended that a resubmission should present a cost-minimisation analysis against other existing combination

regimens used in the proposed setting, such as FOLFOX and FOLFIRI.

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

Outcome:

Rejected

7 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.

8 Sponsor's Comment

The sponsor had no comment.