**Cost-effectiveness of pegylated liposomal irinotecan (Onivyde®), in combination with 5-fluorouracil and leucovorin, for the treatment of adult patients with metastatic adenocarcinoma of the pancreas, that has progressed following gemcitabine-based therapy**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pegylated liposomal irinotecan (Onivyde®). Following assessment of the Applicant's submission, the NCPE recommends that pegylated liposomal irinotecan (Onivyde®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Servier Laboratories (Ireland) Ltd) Health Technology Assessment dossier on pegylated liposomal irinotecan (Onivyde®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**National Centre for Pharmacoeconomics** **November 2021**

**Summary**

In March 2021, Servier Laboratories (Ireland) Ltd submitted a dossier which investigated the clinical, cost-effectiveness and budget impact of pegylated liposomal irinotecan (peg-IRI), for the treatment of adult patients with metastatic adenocarcinoma of the pancreas, which has progressed following gemcitabine-based chemotherapy. Reimbursement is sought through the Oncology Drug Management System, and the drug is hospital administered.

Peg-IRI is a liposomal formulation of irinotecan. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and induce single-strand DNA lesions which block the DNA replication fork and are responsible for the cytotoxicity. Peg-IRI is not equivalent to non-liposomal irinotecan formulations, and should not be interchanged. Peg-IRI should be administered in combination with 5-fluorouracil (5-FU) and leucovorin (LV), (peg-IRI + 5-FU + LV), at a dose of 70mg/$m^2$ via intravenous infusion, every two weeks. Treatment continues until disease progression or unacceptable toxicity.

Current treatments for metastatic adenocarcinoma of the pancreas, refractory to gemcitabine, include the mFOLFOX regimen (oxaliplatin in combination with 5-FU, and LV), non-liposomal irinotecan-based regimens (such as FOLFIRI), and 5-FU in combination with LV (5-FU + LV). The Applicant only considered 5-FU + LV and mFOLFOX as comparators in the submission.

1. **Comparative effectiveness of pegylated liposomal irinotecan**

Clinical efficacy was examined in the NAPOLI-1 trial. This trial was a randomised, open-label, phase III multicentre three-arm trial comparing peg-IRI + 5-FU + LV to 5-FU + LV, and to peg-IRI monotherapy. Enrolled patients were aged over 18 years, with histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas, and documented metastatic disease with disease progression following gemcitabine or gemcitabine-based therapy. Outcomes were measured in the intention-to-treat (ITT) population. Only results from the relevant comparison of peg-IRI + 5-FU + LV versus 5-FU + LV are presented here. The primary endpoint was overall survival (OS); key secondary endpoints included progression free survival (PFS), and objective response rate. Trial outcomes are summarised

in Table 1. The majority of the patients admitted to the trial were white, male, with a mean age of 62.8 years.

**Table 1: NAPOLI-1 clinical outcomes**

Date of final analysis: 16 November 2015

| Outcome | Peg-IRI + 5-FU + LV (n=117) | 5-FU+ LV (n=119) |
|---|---|---|
| Overall survival (median, months, 95%CI) | 6.2 (4.8, 8.4) | 4.2 (3.3, 5.3) |
| HR for overall survival | 0.75 (95% CI 0.57, 0.99), p=0.039† | |
| Mean overall survival (weeks) | 40.8 | 32.4 |
| Progression Free Survival (median, months, 95%CI) | 3.1 (2.7, 4.2) | 1.5 (1.4, 1.8) |
| HR for progression free survival | 0.57 (95% CI 0.43, 0.76), p<0.0001 | |
| Mean progression free survival (weeks) | 24.7 | 13.6 |
| Objective Response Rate (%, 95%CI) * | 8.6% (3.48, 13.61) | 0.8% (0, 2.48) |

**HR:** hazard ratio; **CI:** confidence intervals; **peg-IRI**: pegylated liposomal irinotecan; **5-FU:** 5-fluorouracil; **LV:** leucovorin

**No complete responses were observed, all responses contributing to the objective response rate were partial responses.*

*† Unstratified HR. Stratified HR 0.63 (95% CI 0.47, 0.85, p=0.002).*

An OS and PFS treatment benefit was seen with peg-IRI + 5-FU + LV versus 5-FU + LV. Outcomes were robust to sensitivity analyses, and were consistent across pre-specified subgroups including differing ethnicities and irinotecan-naïve patients. Patients treated with prior irinotecan may have a poorer response to peg-IRI/5-FU/LV; the summary of product characteristics (SmPC) notes that the benefit of peg-IRI in patients previously treated with an irinotecan-based regimen has not been demonstrated. Objective response rates were higher with peg-IRI + 5-FU + LV; this difference was statistically significant but there were no complete responses in either arm. In terms of quality of life, there was no clinically meaningful change from baseline to week 12 in either arm in global health status or functioning measures.

In the randomised NCT02697058 trial in the Japanese setting (n=79), a benefit in PFS and objective response rates but no OS benefit was seen with peg-IRI + 5-FU + LV versus 5-FU + LV (ITT population). This study had a similar design to NAPOLI-1, although it had PFS as the primary endpoint and a more intensive dosing schedule of 5-FU in the 5-FU + LV arm. The Review Group note that OS outcomes were consistent regardless of Asian ethnicity in the NAPOLI-1 trial. There were some imbalances in patient characteristics in NCT02697058 at baseline which may have impacted survival prognosis, and which the Review Group consider may have favoured the 5-FU + LV arm. More patients in the 5-FU + LV arm received

subsequent treatment, and with different regimens, which may have improved survival in that arm. The Review Group highlight a scenario analysis where patients are censored at next subsequent treatment. OS was consistent with that in the ITT population.

No formal evidence synthesis was conducted as part of the submission. Relative efficacy estimates for the cost-effectiveness model for the comparison of peg-IRI + 5-FU + LV versus 5-FU + LV were derived from the NAPOLI-1 trial. In the absence of direct randomised evidence for a comparison with the mFOLFOX regimen, the Applicant sourced efficacy inputs from a retrospective single-centre observational study in Austria, in patients previously treated with gemcitabine. This study found a PFS advantage for peg-IRI + 5-FU + LV versus oxaliplatin + fluoropyrimidines (a proxy for mFOLFOX), but no statistically significant OS advantage. In the absence of randomisation, or any formal efforts to address imbalances in patient baseline characteristics, the reported hazard ratios amount to a naïve indirect comparison.

**The Review Group highlight further concerns regarding the clinical evidence**

- The control arm treatment of NAPOLI-1 (5-FU + LV), is likely inferior to current clinical practice which mainly uses mFOLFOX or an irinotecan-based regimen. Thus the modest treatment benefit seen in NAPOLI-1 may not be generalisable to clinical practice in Ireland.
- Mean age at diagnosis in the population in Ireland is 71.1 years, compared with a mean age of 62.8 years in the NAPOLI-1 trial. The EPAR notes poorer outcomes in patients aged over 65 years of age, although there was still treatment benefit compared with 5-FU + LV.
- No evidence of a statistically significant improvement in OS with peg-IRI + 5FU + LV versus the current standard of care in Ireland (mFOLFOX) has been presented by the Applicant.
- The source of comparative effectiveness estimates versus mFOLFOX for the cost-effectiveness is a retrospective single-centre observational study, a naïve comparison, which is generally considered insufficiently robust for decision making.
- No irinotecan-containing regimens were included as comparators in the cost-effectiveness model.

- The SmPC notes that no benefit of peg-IRI + 5-FU + LV has been demonstrated in the NAPOLI-1 trial in those with prior exposure to non-liposomal irinotecan. If peg-IRI + 5-FU + LV is made available, it should be restricted to the irinotecan-naïve population.

**2. Safety of pegylated liposomal irinotecan**

In the NAPOLI-1 trial, almost all patients in both arms experienced at least one adverse event (AE), and at least one treatment-emergent AE (TEAE); the majority of these TEAEs were considered related to the study drugs. The incidence of grade ≥3 TEAEs was higher with peg-IRI + 5-FU + LV, (76.9%), compared with the 5-FU + LV arm (56%). There was a greater incidence of TEAEs leading to dose modification (70.9% vs 35.8%), dose delay (61.5% vs 32.1%), dose reduction (33.3% vs 3.7%), and dose discontinuation (11.1% vs 7.5%). The most common TEAEs with peg-IRI + 5-FU + LV were diarrhoea (47%), nausea (45.3%), vomiting (42.7%), fatigue (30.8%), decreased appetite (27.4%), and neutropenia (21.4%). The most common TEAEs with 5-FU + LV were nausea (26.1%), vomiting (16.4%) and fatigue (16.4%), diarrhoea (14.9%), and decreased appetite (11.9%). The most common grade ≥3 AEs with peg-IRI + 5-FU + LV were neutropenia (27%), fatigue (14%), diarrhoea (13%), vomiting (11%), anaemia (9%), and nausea (8%).

The SmPC recommends a reduced starting dose of peg-IRI (50mg/$m^2$) for patients known to be homozygous for the UGT1A1*28 allele. A dose increase to 70mg/$m^2$ should be considered if tolerated in subsequent cycles.

Overall the safety profile of peg-IRI + 5FU + LV is worse than that of 5FU + LV. The relative safety profile versus the comparators of interest in the Irish setting is unknown. The EPAR notes that the safety profile of non-liposomal irinotecan is well established, and no unexpected safety findings have so far emerged from the liposomal irinotecan development program.

## 3. Cost effectiveness of pegylated liposomal irinotecan

The Applicant presented a *de novo* partitioned survival cost-effectiveness model, to estimate the cost-effectiveness of peg-IRI +5-FU + LV versus 5-FU + LV and mFOLFOX. The population was based on those enrolled in the NAPOLI-1 trial. Subgroups considered included the irinotecan-naïve population and those with a high Cancer-antigen-19 level at baseline. The cost-effectiveness model included four mutually exclusive health states: progression-free on-treatment, progression-free off-treatment, post-progression, and death. The model had a lifetime horizon of five years, reflecting the poor prognosis for patients with metastatic pancreatic cancer. The perspective was that of the HSE.

The treatment effects captured by the cost-effectiveness model were the delay of disease progression and death. The key efficacy inputs to the model were PFS, time on treatment, and OS. Despite the Kaplan-Meier data being fully mature, the Applicant chose to extrapolate the data using parametric curves, which over-estimated the PFS and OS benefit with peg-IRI + 5FU + LV versus 5FU + LV, when compared to the NAPOLI-1 data.

Costs were sourced from the literature. Costs were included for drug acquisition, administration, adverse events, subsequent treatments, and palliative care. The Applicant updated a number of inputs based on feedback from the Review Group. Utility values were applied to each health state, and additional utility penalty for AEs was applied separately. All utility values were sourced from the literature.

The outcomes of the Applicant base case model are provided in
Table 2. The Review Group made a number of changes to the cost-effectiveness model to generate an adjusted base case. The Review Group applied the fully mature Kaplan-Meier data directly in their adjusted base case, censoring the only patient remaining alive in the comparator arm. The adjustment for background mortality was removed, as all-cause mortality was captured in the mature Kaplan-Meier data from the NAPOLI-1 trial. The outcomes of the Review Group adjusted base case are provided in Table 3.

**Table 2 Cost-effectiveness model outcomes (Applicant base case)**

| Technologies | Total Costs (€) | Total QALYs | Incremental Costs (€) | Incremental QALYs | Pairwise ICERs (€/QALY) |
|---|---|---|---|---|---|
| **ITT population** | | | | | |
| Peg-IRI + 5-FU + LV | 58,947 | 0.589 | - | - | - |
| 5-FU + LV | 34,730 | 0.429 | 24,216 | 0.160 | **151,098** |
| mFOLFOX | 34,515 | 0.401 | 24,431 | 0.188 | **130,093** |

**QALY**: Quality Adjusted Life Year; **ICER**: Incremental Cost-Effectiveness Ratio; **peg-IRI**: pegylated liposomal irinotecan; **5-FU**: 5-Fluorouracil; **LV**: Leucovorin (Folinic acid); m**FOLFOX**: Leucovorin, 5-fluorouracil, and oxaliplatin.
Notes: Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at the list price of all components of the regimen; further discounts on 5-FU and LV may be available to hospitals. Outcomes were consistent in the irinotecan-naïve population (results not shown).

**Table 3 Cost-effectiveness model outcomes (Review Group adjusted base case)**

| Technologies | Total Costs (€) | Total QALYs | Incremental Costs (€) | Incremental QALYs | Pairwise ICERs (€/QALY) |
|---|---|---|---|---|---|
| **ITT population** | | | | | |
| Peg-IRI + 5-FU + LV | 58,235 | 0.557 | - | - | - |
| 5-FU + LV | 36,171 | 0.440 | 22,063 | 0.117 | **189,201** |
| mFOLFOX | 34,080 | 0.399 | 24,155 | 0.158 | **152,971** |

**QALY**: Quality Adjusted Life Year; **ICER**: Incremental Cost-Effectiveness Ratio; **peg-IRI**: pegylated liposomal irinotecan; **5-FU**: 5-Fluorouracil; **LV**: Leucovorin (Folinic acid); m**FOLFOX**: Leucovorin, 5-fluorouracil, and oxaliplatin.
Notes: Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at the list price of all components of the regimen; further discounts on 5-FU and LV may be available to hospitals. Outcomes were consistent in the irinotecan-naïve population (results not shown).

In both the Applicant and the Review Group adjusted base case, the probability of cost-effectiveness is 0% at both the €20,000 and €45,000 per QALY thresholds.

Utility in the progression free state and assumptions around relative dose intensity were the primary drivers of uncertainty for the comparison with 5-FU + LV. For the comparison with mFOLFOX, the primary drivers were the hazard ratios for PFS and OS sourced from the literature.

## 4. Budget impact of pegylated liposomal irinotecan

The price to wholesaler of a single 43mg vial of peg-IRI is €817.11. The Review Group estimate a treatment cost with peg-IRI + 5FU + LV of €24,517 (ex VAT) per patient, with the bulk of that cost attributable to peg-IRI. The Applicant assumes that 10 patients will be treated in year 1, rising to 62 per annum by year 5, leading to a 5-year cumulative gross budget impact of €4.86 million, and a 5-year cumulative net budget impact of €4.34 million (including VAT). In the Review Groups adjusted base case, there is a slightly higher number of patients treated, leading to a 5-year cumulative gross budget impact of €5.84 million, and

a 5-year cumulative net budget impact of €5.29 million (including VAT). The Review Group highlight that by year 5, the gross budget impact is close to €2 million annually.

A scenario including additional costs and cost offsets was also presented; costs such as administration, medical resource use, AEs, and end of life were included. These costs are the derived from the cost-effectiveness model. The Applicant has estimated the additional cost of the peg-IRI + 5-FU + LV regimen to be €4,933 per patient per treatment course.

5. **Patient submissions**

No patient organisation submission was received.

**6. Conclusion**

The NCPE recommends that peg-IRI + 5FU + LV not be considered for reimbursement*. There is no direct, prospective, comparative evidence versus a comparator of interest in the Irish setting, namely mFOLFOX. Relative efficacy estimates versus mFOLFOX were derived from observational evidence, which did not show a statistically significant OS benefit. There is no direct evidence versus irinotecan-based comparators and evidence from NAPOLI-1 suggests there is no benefit in patients who are previously treated with irinotecan. The Applicant has not demonstrated any treatment advantage in terms of safety or quality of life.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods Act) 2013.