NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pegylated liposomal irinotecan in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using pegylated liposomal irinotecan in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 6 December 2016

Second appraisal committee meeting: 31 January 2017

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Pegylated liposomal irinotecan, in combination with 5-fluorouracil and leucovorin, is not recommended within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with pegylated liposomal irinotecan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Pegylated liposomal irinotecan (also referred to as nal-iri; Onivyde, Shire) consists of the anticancer drug irinotecan contained within tiny fat particles called nanoliposomes. The nanoliposomes are expected to accumulate in the tumour and release the irinotecan slowly. Irinotecan blocks an enzyme called topoisomerase I, which causes DNA strands to break. This stops the cancer cells dividing and they eventually die.
Marketing authorisation	Pegylated liposomal irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin (LV), has a marketing authorisation for the treatment of metastatic adenocarcinoma of the pancreasin adults whose disease has progressed after gemcitabine-based therapy.
Adverse reactions	The company submission states the following as common adverse events for pegylated liposomal irinotecan plus 5-FU and LV: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, asthenia, anaemia, stomatitis and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Intravenous infusion. 80 mg/m^2 pegylated liposomal irinotecan, 400 mg/m^2 LV, followed by 2400 mg/m^2 5-FU over 46 hours given every 2 weeks.
Price	£615.35 per 50 mg vial (company submission). Cost per 2-week treatment cycle for pegylated liposomal irinotecan is £1,846.05 based on 3 vials per dose. The company has agreed a patient access scheme with the Department of Health. If pegylated liposomal irinotecan plus 5-FU and LV had been recommended, this scheme would provide a simple discount to the list price of pegylated liposomal irinotecan plus 5-FU and LV with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Shire and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of pegylated liposomal irinotecan plus 5–fluorouracil (5-FU) and leucovorin (LV), having considered evidence on the nature of pancreatic cancer and the value placed on the benefits of liposomal irinotecan plus 5-FU and LV by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and practice

Unmet need

4.1 The committee heard from the clinical and patient experts that metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine is associated with a poor prognosis because there are few treatments available. Survival may be less than 6 months. It heard from the patient experts that diagnosis is devastating and that symptoms, which include weight loss, pain, depression and anixety, can be debilitating and difficult to manage. The committee recognised that extension to life and also quality of life were therefore very important to people with this condition. The committee understood that there have been few new treatments in this area. The committee concluded that the prognosis for people with metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine is poor and that current treatments are limited in efficacy. It therefore recognised the value of additional treatment options.

Treatment pathway

4.2 The committee noted that the treatment options for patients with untreated metastatic pancreatic cancer include curative surgery (only suitable for 10–20% of the population), gemcitabine as recommended in NICE's technology appraisal guidance on gemcitabine for treating pancreatic cancer or FOLFIRINOX (folinic acid, 5-FU, irinotecan, oxaliplatin). Treatment received at this stage would affect subsequent treatment. The committee understood from the clinical expert that oxaliplatin plus 5-FU and LV or capecitabine monotherapy are used in clinical practice in England after gemcitabine treatment, and that 5-FU plus LV therapy is rarely used. The committee also heard from the clinical expert that treatment decisions take into account the balance between the risk and severity of adverse events and the effectiveness of treatment, and that double and triple therapies are preferred to monotherapies if the adverse events are tolerable. The clinical and patient experts emphasised the importance of patient choice in making these treatment decisions. The committee agreed with the company, the evidence review group (ERG) and advice from the clinical expert that the most appropriate comparator for pegylated liposomal irinotecan plus 5-FU and LV in NHS practice would be oxaliplatin plus 5-FU and LV. The committee concluded that an alternative treatment to oxaliplatin plus 5-FU and LV would be of value.

Clinical effectiveness

4.3 The committee considered the clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV. It noted that the NAPOLI-1 trial showed pegylated liposomal irinotecan plus 5-FU and LV to have statistically significantly longer overall survival than 5-FU plus LV (6.2 months; 95% confidence interval [CI] 4.8 to 8.4 for pegylated liposomal irinotecan plus 5-FU and LV compared with 4.2 months; 95% CI 3.3 to 5.3 for 5-FU plus LV [May 2015 cut-off; final cut-off data were also presented but are academic in confidence so

cannot be reported here]) and progression-free survival (3.1 months; 95% CI 2.7 to 4.2, compared with 1.5 months; 95% CI 1.4 to 1.8, p=0.0001). The committee heard from the clinical expert that for ovarian cancer the nanoliposomal particle delivery system has been shown to have better effectiveness than equivalent treatments without the delivery system and the same could apply to pegylated liposomal irinotecan plus 5-FU and LV compared with irinotecan. The committee also understood that combining therapies increased the effectiveness of the treatment but may also increase the adverse events. In NAPOLI-1 treatment-emergent serious adverse events were more common in the pegylated liposomal irinotecan plus 5-FU and LV group than in the 5-FU plus LV group (47.9% compared with 44.8%). The committee noted that the health-related quality of life data collected in NAPOLI-1 showed no real differences at 6 weeks and 12 weeks, suggesting that there was no negative effect on health-related quality of life. The committee concluded that pegylated liposomal irinotecan plus 5-FU and LV was more clinically effective than 5-FU plus LV alone but was associated with more treatment-emergent serious adverse events.

Company's indirect treatment comparison with oxaliplatin plus 5-FU and LV

4.4 The committee noted that the company considered an indirect comparison was needed to compare the clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV. But the company considered an indirect comparison could not be done because the trials were too heterogeneous, with issues including different trial populations, incomplete data on patient baseline characteristics and different oxaliplatin plus 5-FU and LV regimens in the oxaliplatin trials. However, the company did an indirect comparison to generate hazard ratios in order to plot the oxaliplatin plus 5-FU and LV Kaplan–Meier curve, using the 5-FU plus LV curve from NAPOLI-1, to compare cost effectiveness between the treatments. The committee acknowledged that the validity of the results relied on an assumption of proportional hazards

between treatments for overall survival and progression-free survival for all the trials included in the mixed treatment comparison, and that the company and ERG stated this was not true for NAPOLI-1. The committee also noted that given the uncertainties in the indirect treatment comparison the ERG had reviewed the literature and concluded that, in general, the progression-free survival and overall survival estimates appeared very similar for oxaliplatin plus 5-FU and LV and for pegylated liposomal irinotecan plus 5-FU and LV. The clinical expert commented that the oxaliplatin plus 5-FU and LV combination would be more effective than 5-FU plus LV, but the relative effectiveness compared with pegylated liposomal irinotecan plus 5-FU and LV was difficult to estimate. However, the company considered that the proportional hazards assumption (that the relative risk of an event is fixed irrespective of time) held for the overall survival data up to 21 months into the trial, at which point the Kaplan–Meier curves crossed. The committee discussed the overall survival and progression-free survival seen in NAPOLI-1, and considered that for both there was a violation of the proportional hazards assumption. Recognising the uncertainty in the indirect comparison the committee concluded that the company's hazard ratios could not be considered reliable for comparing the relative treatment effect of pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV, but the clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV could be considered broadly similar to oxaliplatin plus 5-FU and LV.

Cost effectiveness

4.5 The committee considered the company's de novo model, the associated assumptions and the critique presented by the ERG. It considered that the structure of the company's model appropriately captured the main aspects of metastatic adenocarcinoma of the pancreas after gemcitabine treatment and concluded that it was appropriate to use for decision-making.

Use of parametric modelling

4.6 The committee considered how the company had modelled overall survival, progression-free survival and time to treatment failure data using parametric modelling (a log-normal model for the company's base case). It noted that for comparing pegylated liposomal irinotecan plus 5-FU and LV with 5-FU plus LV the company had assumed that proportional hazards applied (the relative risk of an event is fixed irrespective of time) but had fitted a log-normal curve to both the pegylated liposomal irinotecan plus 5-FU and LV and 5-FU plus LV groups. The ERG indicated that the proportional hazards assumption is not compatible with log-normal parametric models because accelerated failure time models do not produce a single hazard ratio. The ERG also noted that the time ratio adjustment could not be done because the accelerated failure time adjustment was also violated when examining the NAPOLI-1 data. The committee heard that the ERG considered curve fitting to be inappropriate because most of the data from the trial were complete. It also heard that of the 3 approaches explored by the ERG, the committee agreed with the ERG that the preferred method used the Kaplan–Meier data directly from the trial with extrapolation for the 1 remaining patient in the 5-FU plus LV group. The committee also noted that the company did not provide a biological rationale for using the log-normal model, which overestimated progression-free survival for both groups in the trial for the first 4 months, and underestimated survival from 6 months onwards. The Committee was aware that the company's model estimated a 4.8% greater progression-free survival gain than the trial data when comparing pegylated liposomal irinotecan plus 5-FU and LV with 5-FU plus LV. Also, modelling time to treatment underestimated the overall time on treatment (15% for the 5-FU plus LV group and 1.4% for the pegylated liposomal irinotecan plus 5-FU and LV group) particularly for the first 15 months of the trial. The ERG considered that the log-normal parametric model, when applied to the time on treatment data, overestimated the proportion of patients in the

progression-free state. The committee also noted that the modelling showed that benefit continued even after the patient had stopped treatment. When comparing survival on pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV, the committee heard from the ERG that using the company's indirect treatment comparison hazard ratios (assuming proportional hazards) to adjust the parametric curves was unreliable because of the issues with the indirect treatment comparison (see section 4.4). The committee concluded that because the data for progression-free survival and time on treatment are complete and virtually complete for overall survival, using the Kaplan–Meier data from NAPOLI-1 was more appropriate than the company's parametric modelling.

Cost-related model assumptions

4.7 The committee considered the costs of pegylated liposomal irinotecan plus 5-FU and LV and the comparators 5-FU plus LV and oxaliplatin plus 5-FU and LV included in the company's model. It noted that the company model had assumed that a reduced or missed dose because of adverse events in NAPOLI-1 would reduce drug acquisition costs. The committee heard from the clinical expert that in clinical practice parenteral treatments are often prepared by the pharmacy department when the patient is seen at the outpatient clinic and not when the patient is treated. Therefore planned treatment variations can be accounted for when treatment is given but are difficult to predict in advance. The committee concluded that it was not appropriate to assume that cost savings from dose reductions would always be accounted for in clinical practice and that full costing should be assumed in the base case.

4.8 The committee considered the costs of the generic comparators used in the company's model. It noted that the company used the list prices from the British national formulary, rather than taking costs from the Electronic Market Information Tool (eMit), which provides details of average prices

paid by NHS hospitals in England for generic drugs. The committee also heard from the ERG that the company had assumed that only one vial size is available for each generic drug; 500 mg for 5-FU, 50 mg for oxaliplatin and 50 mg for LV. However, information in the eMit database shows that there are multiple vial sizes for each of these generic drugs and that generally the larger the vial, the lower the cost per mg of the drug. The committee noted that the ERG had recalculated the average cost per dose of the intervention and the comparators using prices from the eMit, taking into account the range of vial sizes available for the generic drugs and the best combination of vial sizes for the required dose. The committee concluded that it was not appropriate to assume use of the smallest sized vials in the company's model and that the ERG's method of calculating costs was more appropriate.

Utility values used in the company's model

4.9 The committee noted that health-related quality of life data were collected in NAPOLI-1 but these were incomplete and were not used in the company's economic modelling. It was aware that the company used EQ-5D values that were weighted using the general US population tariff but adjusted for the UK population, and incorporated disutility values to account for adverse events of treatment. The company's health state utility values for all treatments were 0.742 for the pre-progression health state and 0.671 for the post-progression health state, taken from the NICE technology appraisal guidance on paclitaxel as albumin-bound nanoparticles for untreated pancreatic cancer. It also noted that the company used the same utility values regardless of the treatment the patient received (pegylated liposomal irinotecan plus 5-FU and LV, oxaliplatin plus 5-FU and LV, or 5-FU plus LV). The committee heard that the ERG considered these values to overestimate patient health-related quality of life because they were taken from a population who had not had treatment and who were likely to be in better health. The committee heard from the company that it considered the performance status of patients in

NAPOLI-1 to be similar to the population in CA046 (the trial considered in the NICE technology appraisal guidance on paclitaxel as albumin-bound nanoparticles for untreated pancreatic cancer), because the patients in NAPOLI-1 were fitter than those generally seen in clinical practice. Also, the distribution of the performance status scores was similar between the studies. It also heard from the clinical expert that the utility values used by the ERG were from people with gastric cancer who may not be comparable to people with pancreatic cancer. The committee concluded that although there was uncertainty about the most appropriate utility values to use for a second-line treatment population with pancreatic cancer, the values used by the company were acceptable for decision-making.

Most plausible ICER considerations

4.10 The committee considered the most plausible incremental cost-effectiveness ratio (ICER) for pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV, including the patient access scheme. The committee noted that the company's base-case ICER including the patient access scheme was £96,591 per quality-adjusted life year (QALY) gained and that the ERG's exploratory ICER, combining all ERG scenarios, was £162,887 per QALY gained. When including the committee's preferred extrapolation of survival with the remaining assumptions taken from the company's analyses the ICER was £137,354 per QALY gained. However, the committee considered that all the changes, except the ERG's preferred health state utility values, should be included in the base case. It therefore concluded that taking into account all of the ICERs presented, the ICER for pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV was over £100,000 per QALY gained. The committee considered that the ICER was considerably higher than would normally be considered a cost-effective use of NHS resources.

4.11 The committee considered the most plausible ICER for pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin plus 5-FU and LV, including the patient access scheme for pegylated liposomal irinotecan. The committee noted that the company's base-case ICER including the patient access scheme was £54,412 per QALY gained. It also noted that the ERG's exploratory ICER, combining all the ERG's scenarios and the committee's preferred extrapolation of survival was £106,898 per QALY gained and £64,526 per QALY gained. The committee still recognised the uncertainty about the pre-progression time on treatment for oxaliplatin plus 5-FU and LV, but even taking this into account and using the company's preferred utility estimates the ICER would be in excess of £50,000 per QALY gained. The committee also noted that because of the uncertain clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin plus 5-FU and LV, particularly with the total QALYs for oxaliplatin plus 5-FU and LV being lower then 5-FU plus LV in the company's submission, the ERG did further exploratory analyses altering the QALY difference between the 2 treatments. When taking into account these scenarios the ICER ranged from £201,019 (when the total QALYs for oxaliplatin plus 5-FU and LV were 10% less than pegylated liposomal irinotecan plus 5-FU and LV) to pegylated liposomal irinotecan plus 5-FU and LV being dominated (that is, less effective and more expensive than oxaliplatin plus 5-FU and LV when the total QALYs for oxaliplatin plus 5-FU and LV were 10% more). The committee concluded that although the analyses comparing pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV were subject to considerable uncertainty, it was confident that pegylated liposomal irinotecan plus 5-FU and LV would not be considered a cost-effective use of NHS resources.

End-of-life considerations

4.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The committee heard from the clinical and patient experts that the life expectancy of patients with metastatic adenocarcinoma of the pancreas after gemcitabine treatment was considerably less than 2 years. It also heard from the company that people with metastatic pancreatic cancer have a median survival of 2.8 to 5.7 months. The committee concluded that the criterion for short life expectancy was met.

4.13 The committee considered the criterion for extension to life. It noted that the median extension in overall survival in NAPOLI-1for pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV was 1.9 months. It also considered the results of the company's log-normal model showing a mean overall survival of 2.5 months for this comparison. However, the committee noted that it's preferred estimate of overall survival (using the Kaplan–Meier data and extrapolation for 1 patient in the 5-FU plus LV comparator group who had yet to have an event) was 1.8 months. It also noted that both the company and the ERG were unable to produce a reliable estimate of the difference in overall survival between pegylated liposomal irinotecan plus 5-FU and LV and oxaliplatin plus 5-FU and LV (the most appropriate comparator), but when comparing 3 trials of oxaliplatin plus 5-FU and LV the median overall survival was similar to that reported for pegylated liposomal irinotecan plus 5-FU and LV in NAPOLI-1. The committee also noted that when the company fitted log-logistic models to the NAPOLI-1 data but did not extrapolate for the 1 remaining patient, in the 5-FU plus LV group, the overall survival gain was 2.2 months. The committee considered that the overall survival gain was likely to be less than 2.2 months given that the surviving patient was in the 5-FU plus LV comparator group of the trial and that 5-FU plus LV

was the wrong comparator. The committee did not accept that the extension to life criterion was met, even taking into consideration the very short life expectancy for this population.

4.14 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee understood that the company was not making a case for pegylated liposomal irinotecan plus 5-FU and LV to be considered for funding through the Cancer Drugs Fund. The committee considered that the most plausible ICERs for pegylated liposomal irinotecan plus 5-FU and LV (see sections 4.10 and 4.11) for both comparisons were substantially higher than the range normally considered a cost-effective use of NHS resources. Therefore pegylated liposomal irinotecan plus 5-FU and LV did not have plausible potential to satisfy the criteria for routine use. The committee also considered that although there were uncertainties in the evidence for this appraisal, the clinical effectiveness evidence from NAPOLI-1 was complete (see section 4.6). It heard from the company that there were no ongoing trials that could be used to inform the clinical uncertainty around the comparison with oxaliplatin plus 5-FU and LV and therefore a subsequent update of the guidance. The committee concluded that pegylated liposomal irinotecan plus 5-FU and LV did not meet the criteria to be considered for funding through the Cancer Drugs Fund.

Innovation

4.15 The committee discussed whether pegylated liposomal irinotecan plus 5-FU and LV was innovative in its potential to make a significant and substantial impact on health-related benefits. It heard from the clinical and patient experts that there were few options for treating metastatic adenocarcinoma of the pancreas and that pegylated liposomal irinotecan plus 5-FU and LV would provide another option. However, the committee concluded that having an extra treatment option for treating metastatic

adenocarcinoma of the pancreas did not mean that pegylated liposomal irinotecan plus 5-FU and LV was innovative. It also concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine**	**Section**
Key conclusion		
Pegylated liposomal irinotecan, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), is not recommended within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy.		1.1
The committee considered that the NAPOLI-1 trial showed pegylated liposomal irinotecan plus 5-FU and LV has a statistically significantly longer overall survival than 5-FU plus LV.		4.3
The company considered that an indirect comparison to compare pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV could not be done because the trials were too heterogeneous. However, the company did an indirect comparison to generate hazard ratios, so it could then compare the cost effectiveness of the treatments.		4.4
Taking into account all of the incremental cost-effectiveness ratio (ICERs) presented, the committee concluded that the ICER for pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV was over £100,000 per quality-adjusted life year (QALY)		4.10

gained. The committee concluded that although the analyses comparing pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV were subject to considerable uncertainty, it was confident that pegylated liposomal irinotecan plus 5-FU and LV would not be considered a cost-effective use of NHS resources.		4.11
Current practice		
Clinical need of patients, including the availability of alternative treatments	Metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine treatment is associated with a poor prognosis because there are few treatments available, and survival may be less than 6 months. Current treatments are limited in efficacy so there is value in more treatment options in this area.	4.1
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the clinical and patient experts that there were few options for treating metastatic adenocarcinoma of the pancreas and that pegylated liposomal irinotecan plus 5-FU and LV would provide another option. However, the committee concluded that having an extra treatment option did not mean that pegylated liposomal irinotecan plus 5-FU and LV was innovative. It also concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.	4.14
What is the position of the treatment in the pathway of care for the condition?	The committee understood from the clinical expert that oxaliplatin plus 5-FU and LV and capecitabine monotherapy are used in clinical practice in England after gemcitabine treatment. The committee agreed with the company, ERG and advice from the clinical expert that the most appropriate treatment comparator for pegylated liposomal irinotecan plus 5-FU and LV in NHS practice would be oxaliplatin plus 5-FU and LV.	4.2

Adverse reactions	In the NAPOLI-1 trial, treatment-emergent serious adverse events were more common in the pegylated liposomal irinotecan plus 5-FU and LV group than in the 5-FU plus LV group (47.9% compared with 44.8%). The committee noted that health-related quality of life data were collected in NAPOLI-1 and that the results at 6 weeks and 12 weeks showed no real differences, suggesting no negative effect on health-related quality of life.	4.3
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company's submission presented clinical-effectiveness evidence from the NAPOLI-1 trial for the comparison of pegylated liposomal irinotecan plus 5-FU and LV with 5-FU plus LV. The company considered that an indirect comparison was needed to determine the clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin plus 5-FU and LV, but that this was not feasible because the trials were too heterogeneous.	4.3 4.4
Relevance to general clinical practice in the NHS	The patients in NAPOLI-1 were fitter than those generally seen in clinical practice.	4.9

Uncertainties generated by the evidence	The committee noted that given the uncertainties inherent in the indirect treatment comparison the ERG reviewed the literature and concluded that, in general, the progression-free survival and overall survival estimates appeared very similar for oxaliplatin plus 5-FU and LV and pegylated liposomal irinotecan plus 5-FU and LV. The committee also noted that the relative effectiveness of oxaliplatin plus 5-FU and LV compared with pegylated liposomal irinotecan plus 5-FU and LV was difficult to estimate.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	N/A	–

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The median extension in overall survival in NAPOLI-1 for pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV was 1.9 months. Both the company and the ERG were unable to produce a reliable estimate of the difference in overall survival between pegylated liposomal irinotecan plus 5-FU and LV and oxaliplatin plus 5-FU and LV, but when comparing 3 trials of oxaliplatin plus 5-FU and LV the median overall survival was similar to that reported for pegylated liposomal irinotecan plus 5-FU and LV in NAPOLI-1.	4.13
Evidence for cost effectiveness		
Availability and nature of evidence	The company submitted a de novo economic model to estimate the cost effectiveness of pegylated liposomal irinotecan plus 5-FU and LV, compared with 5-FU plus LV and with oxaliplatin plus 5-FU and LV, in people with metastatic adenocarcinoma of the pancreas after gemcitabine treatment. The company used an indirect treatment comparison to estimate overall survival, progression-free survival and time-on-treatment curves for the comparison with oxaliplatin plus 5-FU and LV.	4.5 4.6

Uncertainties around and plausibility of assumptions and inputs in the economic model	The company made assumptions relating to the costs and survival estimates. The committee concluded that because the data were complete for progression-free survival and time on treatment, and virtually complete for overall survival, using the Kaplan–Meier data from NAPOLI-1 was more appropriate than the company's use of parametric modelling. The committee concluded that it was not appropriate to assume dose reductions would always be applicable in the company's model and that full costing should be assumed in the base case. It also concluded that it was not appropriate to assume the use of the smallest sized vials in the company's model and that the ERG's method of calculating costs was more appropriate.	4.5 to 4.8

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee concluded that although there was uncertainty relating to the most appropriate utility values for a second-line treatment population with pancreatic cancer, the values used by the company were acceptable for decision-making. The committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.	4.9 4.15
Are there specific groups of people for whom the technology is particularly cost effective?	N/A	–

What are the key drivers of cost effectiveness?	For the comparison of pegylated liposomal irinotecan plus 5-FU and LV with 5-FU plus LV the committee considered that all the changes, except the ERG's preferred health state utility values, should be included in the base case. The committee therefore concluded that the ICER for pegylated liposomal irinotecan plus 5-FU and LV, compared with 5-FU plus LV, was over £100,000 per QALY gained. For the comparison of pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV, the ERG carried out scenarios altering the QALY difference between the 2 treatments. When taking into account these scenarios, the ICER ranged from £201,020 per QALY gained (when the total QALYs for oxaliplatin plus 5-FU and LV were 10% less than pegylated liposomal irinotecan plus 5-FU and LV) to pegylated liposomal irinotecan plus 5-FU and LV being dominated (when the total QALYs for oxaliplatin plus 5-FU and LV were 10% more).	4.10 4.11

Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that taking into account all of the ICERs presented, the ICER for pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU plus LV was over £100,000 per QALY gained. For the comparison of pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV the committee recognised the uncertainty regarding the pre-progression time on treatment for oxaliplatin plus 5-FU and LV, but even omitting this assumption and using the company's preferred utility estimates the ICER would be in excess of £50,000 per QALY gained.	4.10 4.11
Additional factors taken into account		
Patient access schemes (PPRS)	The committee considered analyses incorporating the confidential patient access scheme for pegylated liposomal irinotecan plus 5-FU and LV.	4.10 and 4.11

End-of-life considerations	The committee concluded that the criterion for short life expectancy was met. However, pegylated liposomal irinotecan plus 5-FU and LV survival estimates from the trial and model showed that the criterion for extension to life was not met for the comparison with either 5-FU plus LV or oxaliplatin plus 5-FU and LV. The committee noted that when comparing 3 trials of oxaliplatin plus 5-FU and LV the median overall survival was similar to that reported for pegylated liposomal irinotecan plus 5-FU and LV in NAPOLI-1. Therefore, the committee concluded that pegylated liposomal irinotecan plus 5-FU and LV did not meet the NICE supplementary advice criteria to be considered as a life-extending, end-of-life treatment.	4.12 to 4.13
Equalities considerations and social value judgements	No equalities issues were raised during this appraisal.	-

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based

on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, appraisal committee
August 2016

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Caroline Hall
Technical Lead

Sally Doss
Technical Adviser

Kate Moore

Project Manager

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