NICE National Institute for Health and Care Excellence

NICE guidance

Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

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

Summary of pegylated liposomal irinotecan

Description of the technology	Pegylated liposomal irinotecan (Onivyde, Shire) consists of the anticancer drug irinotecan contained within tiny fat particles called nanoliposomes. The nanoliposomes accumulate in the tumour and release 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 treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy.
Adverse reactions	The company submission includes 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 of 80 mg/m^2 pegylated liposomal irinotecan, 400 mg/m^2 LV, followed by 2,400 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 considered evidence submitted by Shire and a review of this submission by the evidence review group. 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 pegylated 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 anxiety, 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. It 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 untreated metastatic pancreatic cancer include curative surgery (only suitable for 10 to 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

treatment later. 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 alone 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. 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 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, although it acknowledged that 5-FU plus LV is rarely used in clinical practice, and is therefore not established practice. It noted that in the NAPOLI-1 trial, overall survival on pegylated liposomal irinotecan plus 5-FU and LV was statistically significantly longer than on 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]). Progression-free survival was also statistically significantly longer than on 5-FU plus LV (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 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 (that is, events that first appear during treatment, or worsen during treatment) 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 between the groups at 6 weeks and 12 weeks, suggesting that there was no negative effect of pegylated liposomal irinotecan 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 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 company considered that a formal indirect comparison of the clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV was not appropriate because the trials were too heterogeneous. Issues included different trial populations, incomplete data on patient baseline characteristics and different oxaliplatin plus 5-FU and LV regimens in the oxaliplatin trials. But, to compare the cost effectiveness of the treatments, the company did an indirect comparison which generated hazard ratios to plot the oxaliplatin plus 5-FU and LV Kaplan–Meier curve, using the 5-FU plus LV curve from NAPOLI-1. The committee acknowledged that the validity of the results relied on an assumption of proportional hazards (that is, the relative risk of an event is fixed irrespective of time) 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 considered that for both overall survival and progression-free survival there was a violation of the proportional hazards assumption.

4.5 The committee also noted that the ERG had reviewed the literature given the uncertainties in the indirect treatment comparison. The ERG 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 oxaliplatin plus 5-FU and LV would be more effective than 5-FU plus LV, but its relative effectiveness compared with pegylated liposomal irinotecan plus 5-FU and LV was difficult to estimate. Recognising the uncertainty in the indirect comparison,

the committee concluded that the company's approach 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. However 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

4.6 The committee considered the company's de novo model, the associated assumptions and the ERG's critique. It considered that the structure of the company's model 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

4.7 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). The company assumed that proportional hazards applied, but had fitted a log-normal curve to the results from both the pegylated liposomal irinotecan plus 5-FU and LV and the 5-FU plus LV groups. The committee heard that the ERG considered curve fitting to be inappropriate because most of the trial data were complete. It agreed with the ERG that of the 3 approaches explored, 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 noted that the company did not provide a biological rationale for using the log-normal model, which 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. Modelling time to treatment failure also underestimated the overall time on treatment and the company's modelling showed that benefit continued even after the patient had stopped treatment. 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 using the company's parametric modelling.

4.8 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 also noted that the total quality-adjusted life years (QALYs) for oxaliplatin plus 5-FU and LV were significantly lower than for 5-FU plus LV in the company's analysis. It acknowledged that this result was not in agreement with comments from the clinical expert, who stated that oxaliplatin plus 5-FU and LV is the preferred option; it is more clinically effective than 5-FU plus LV and is standard clinical practice in the NHS. The committee concluded that the company's approach for modelling survival to compare pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV gave clinically implausible results and lacked robustness for decision-making.

Cost-related model assumptions

4.9 The committee considered the costs of pegylated liposomal irinotecan plus 5-FU and LV and of the comparators (5-FU plus LV and oxaliplatin plus 5-FU and LV) included in the company's model. It noted that the company's model 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.

4.10 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 1 vial size is available for each generic

drug; 500 mg for 5-FU, 50 mg for oxaliplatin and 50 mg for LV. However, 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 eMit prices, taking into account the range of vial sizes available for the generic drugs and the best combination of vial sizes for the dose needed. 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

4.11 The committee noted that health-related quality-of-life data were collected in NAPOLI-1 but these were incomplete and not used in the company's economic modelling. 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 NICE's technology appraisal guidance on paclitaxel as albumin-bound nanoparticles for untreated pancreatic cancer. The committee was aware that the EQ-5D values 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. It also noted that the company used the same utility values regardless of the treatment the patient had (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 that of the population in CA046 (the trial considered in NICE's 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. The committee noted that the ERG had explored using utility values from people with gastric cancer, but it heard from the clinical expert that these utility values 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 ICERs

4.12 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 QALY gained. However, the committee considered that all the ERG's amendments, except the ERG's preferred health state utility values, should be included in the base case. The committee noted it did not have an ICER that reflected all of its preferred assumptions. The ERG's exploratory ICER, combining all ERG amendments, was £162,887 per QALY gained. When only amending 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. 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 much higher than would normally be considered a cost-effective use of NHS resources.

4.13 Acknowledging that the analysis in section 4.12 compared pegylated liposomal irinotecan with a treatment (5-FU plus LV) not considered to be established practice in the NHS, the committee considered the most plausible ICER for pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin plus 5-FU and LV (the appropriate comparator), 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 including the committee's preferred extrapolation of survival, was £106,898 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 implausibly lower than 5-FU plus LV in the company's submission (see section 4.8), 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 per QALY gained (when the total QALYs for oxaliplatin plus 5-FU and LV were 10% less than for 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

4.14 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.

4.15 The committee considered the criterion for extension to life. It noted that 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. The committee noted that its 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. 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 would be less than 2.2 months given that the surviving patient was in the 5-FU plus LV group. The committee acknowledged that 5-FU plus LV was not established practice in the NHS, and therefore not the appropriate comparator to assess the end-of-life criteria. Even if it were, the committee did not accept that

the extension to life criterion had been met for this comparison, even taking into consideration the very short life expectancy for this population. 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 did not accept that the extension to life criterion was met for pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin plus 5-FU and LV. The committee concluded that pegylated liposomal irinotecan did not fulfil the criteria for a life-extending treatment at the end of life.

4.16 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 4.12 and 4.13) 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 4.7). 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

4.17 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 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.

5 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 and Helen Tucker
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