# Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine: an Evidence Review Group Perspective of a NICE Single Technology Appraisal

## Running title: Liposomal irinotecan for treating pancreatic cancer after gemcitabine

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# Abstract

The National Institute for Health and Care Excellence (NICE) invited the manufacturer (Shire Pharmaceuticals) of pegylated liposomal irinotecan hydrochloride trihydrate (liposomal irinotecan) to submit clinical and cost-effectiveness evidence for its use in combination with 5-fluorouracil (5-FU) and folic acid/leucovorin (LV) for treating patients with pancreatic cancer following prior treatment with gemcitabine as part of the Institute’s Single Technology Appraisal process. The Liverpool Reviews and Implementation Group at the University of Liverpool was commissioned to act as the Evidence Review Group (ERG). This article presents a summary of the company’s evidence, the ERG review and the resulting NICE guidance (TA440), issued 26 April 2017. Clinical evidence for liposomal irinotecan+5-FU/LV versus 5-FU/LV was derived from 236 patients with metastatic pancreatic cancer in the multinational, open-label randomized controlled NAPOLI-1 trial. Results from analyses of progression-free survival and overall survival showed statistically significant improvements for patients treated with liposomal irinotecan+5-FU/LV compared with those treated with 5-FU/LV. However, 5-FU/LV alone is rarely used in NHS clinical practice for patients with metastatic pancreatic cancer previously treated with gemcitabine. The company, ERG and Appraisal Committee (AC) all agreed that oxaliplatin+5-FU/LV is the most commonly used treatment. Oxaliplatin+5-FU/LV was compared with 5-FU/LV in two trials identified by the company. However, the company and the ERG both considered attempts to compare the efficacy of liposomal irinotecan+5-FU/LV with oxaliplatin+5-FU/LV to be methodologically flawed: not only was there heterogeneity between trials and their populations, but also the proportional hazards assumption required to conduct a robust indirect treatment comparison (ITC) was violated. Nonetheless, data derived from an ITC were used to inform the company’s economic model. Using the discounted patient access scheme price for liposomal irinotecan+5-FU/LV, the company reported an incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained of £54,412 for the comparison with oxaliplatin+5-FU/LV. The ERG considered that the company’s base case cost-effectiveness results for the comparison of liposomal irinotecan+5-FU/LV versus oxaliplatin-5-FU/LV were underestimates and should be interpreted with extreme caution. Following implementation of a number of model amendments, the ERG’s modified exploratory ICER for the comparison of liposomal irinotecan+5-FU/LV versus oxaliplatin-5-FU/LV was £106,898 per QALY gained. The AC accepted the majority of the ERG’s amendments to the model. The AC also highlighted that the total QALYs for oxaliplatin+5-FU/LV were lower than for 5-FU/LV in the company’s model, which the AC considered to be clinically implausible. The AC, therefore, considered results from exploratory analyses, undertaken by the ERG, which included altering the QALY difference between liposomal irinotecan+5-FU/LV and oxaliplatin+5-FU/LV by +/-10%. These analyses resulted in ICERs for the comparison of liposomal irinotecan+5-FU/LV versus oxaliplatin-5-FU/LV of between £201,019 per QALY gained to liposomal irinotecan+5-FU/LV being dominated by oxaliplatin+5-FU/LV. Therefore, despite uncertainty around the clinical effectiveness evidence and cost-effectiveness results, the AC was confident that the ICER was in excess of £50,000 per QALY gained. The final guidance issued by NICE is that liposomal irinotecan+5FU/LV is not recommended within its marketing authorization for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy.

# Key Points

* For patients with metastatic pancreatic cancer who have received prior treatment with gemcitabine, the findings from the NAPOLI-1 trial demonstrate that pegylated liposomal irinotecan hydrochloride trihydrate (liposomal irinotecan) in combination with 5-fluorouracil (5-FU) and folinic acid/leucovorin (LV) (liposomal irinotecan+5-FU/LV) is more efficacious than 5-FU/LV; however, in NHS clinical practice, 5-FU/LV alone is not used to treat patients with metastatic adenocarcinoma of the pancreas who have previously been treated with gemcitabine.
* Attempts to use a conventionally accepted method for conducting an indirect treatment comparison (ITC) to compare the clinical effectiveness of treatment with liposomal irinotecan+5-FU/LV with a more relevant comparator (such as oxaliplatin+5-FU/LV) were considered by both the company (Shire Pharmaceuticals), and by the Evidence Review Group (ERG), to be methodologically flawed.
* In addition to the difficulties in generating robust evidence for clinical effectiveness, the ERG identified a number of areas of concern relating to the way in which the company’s economic model was constructed, in particular the approach taken to the modelling of patient survival. The Appraisal Committee (AC) accepted the majority of the ERG’s modifications to the company’s model.
* Despite recognising that there was considerable uncertainty around the available clinical and cost-effectiveness evidence, the AC was confident that liposomal irinotecan+5-FU/LV would not be a cost-effective use of NHS resources. Liposomal irinotecan+5-FU/LV was not recommended within its marketing authorization for the treatment of patients with metastatic adenocarcinoma of the pancreas, following treatment with gemcitabine.

# 1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organization responsible for providing national guidance to the NHS in England on a range of clinical and public health issues, including the appraisal of new health technologies. The NICE Single Technology Appraisal (STA) process is specifically designed for the appraisal of a single health technology for a single indication, where most of the relevant evidence lies with one manufacturer or sponsor and typically covers new technologies shortly after UK market authorization is granted [1].{National Institute for Health and Clinical Excellence, 2012 #275;National Institute for Health and Clinical Excellence (NICE), 2009 #148} Within the STA process, the manufacturer or sponsor provides a written submission (alongside a decision-analytic model) that summarizes the estimate of the clinical effectiveness and cost-effectiveness of the technology. An external independent organisation (typically, an academic group) known as the Evidence Review Group (ERG), provides a critique of the company’s submission (the ERG report). Consultees, clinical specialists and patient representatives also provide additional information during the appraisal process.

Following a specification developed by NICE (the final scope), the NICE Appraisal Committee (AC) considers the company’s submission, the ERG report and testimonies from experts and stakeholders in order to determine whether the technology represents a clinical- and cost-effective use of NHS resources. All stakeholders and the public have an opportunity to comment on the preliminary guidance issued by NICE in the form of an Appraisal Consultation Document (ACD), after which the AC meets again to produce the final guidance (Final Appraisal Determination [FAD]). The final guidance constitutes a legal obligation for NHS providers in England and Wales to provide a technology that is approved within its licensed indication [1].{National Institute for Health and Clinical Excellence, 2012 #275;National Institute for Health and Clinical Excellence (NICE), 2009 #148}

This article presents a summary of the ERG report for the STA of pegylated liposomal irinotecan hydrochloride trihydrate (hereafter referred to liposomal irinotecan; OnivydeTM), manufactured by Shire Pharmaceuticals) for treating metastatic adenocarcinoma of the pancreas after gemcitabine. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, NICE guidance and comments on each of these) can be found on the NICE website [2].

# 2. The Decision Problem

In 2014, pancreatic cancer was the 11th most common cancer in the UK; there were an estimated 9,618 new cases, accounting for 3% of all new cancer cases [3]. Only 3% of patients diagnosed with pancreatic cancer in England and Wales survive beyond 5 years with little improvement in UK survival rates in the last 40 years [4]. In NHS clinical practice, gemcitabine is the most commonly prescribed first-line chemotherapy for pancreatic cancer [5]. In the NICE scope for this appraisal [6], the population under consideration was described as patients with metastatic adenocarcinoma of the pancreas that has progressed following gemcitabine-based therapy.

The treatment considered in this appraisal was pegylated liposomal irinotecan hydrochloride trihydrate (hereafter referred to as liposomal irinotecan) in combination with 5-fluorouracil (5-FU) and folinic acid/leucovorin (LV). On 19 October 2016, liposomal irinotecan received its marketing authorization from the European Commission. It is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU/LV in adult patients who have progressed following gemcitabine based therapy. At the time of this appraisal (the final NICE scope [6] was issued in February 2016), no second-line treatments for patients who progress following gemcitabine-based therapy were recommended by NICE. Oxaliplatin in combination with 5-FU/LV (oxaliplatin+5-FU/LV), capecitabine monotherapy (a type of fluoropyrimidine monotherapy) or oxaliplatin+capecitabine were used to treat these patients in NHS clinical practice [5]. Oxaliplatin+5-FU/LV, fluoropyrimidine monotherapy and oxaliplatin+capecitabine were all comparators specified in the NICE scope [6].

The scope [6] specified that the clinical and cost-effectiveness of liposomal irinotecan+5-FU/LV should be established within its licensed indication. Relevant measures of clinical effectiveness included overall survival (OS), progression-free survival (PFS), adverse effects of treatment (AEs) and health-related quality of life (HRQoL). The scope [6] also stated that cost-effectiveness results should be presented in terms of the incremental cost per quality-adjusted life year (QALY) gained using a time horizon sufficiently long to reflect differences in costs or outcomes between the technologies and that costs should be considered from an NHS and Personal Social Services (PSS) perspective. No specific subgroups of patients and no potential equity or equality issues were identified.

# 3. Independent Evidence Review Group Report

The evidence provided by the company comprised an initial submission, an economic model and the company’s response to the ERG’s clarification requests. The ERG report comprised a summary and critical review of the evidence for the clinical and cost-effectiveness of the technology provided by the company. The role of the ERG was to:

* Assess whether the company’s submitted evidence conforms to the methodological guidelines issued by NICE;
* Assess whether the company’s interpretation and analyses of the evidence are appropriate;
* Indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform the development of NICE guidance.

## 3.1 Clinical Evidence

The company conducted a systematic review designed to identify studies investigating the effectiveness of liposomal irinotecan+5-FU/LV and/or the comparators listed in the final scope issued by NICE. The company’s review included 13 randomized controlled trials (RCTs) [7-19]. However, only one RCT (the NAPOLI-1 trial [18]) included patients treated with liposomal irinotecan+5-FU/LV. This multinational phase III open-label RCT compared the efficacy and safety of liposomal irinotecan+5-FU/LV versus 5-FU/LV and also liposomal irinotecan monotherapy versus 5-FU/LV in 417 patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy. Only the comparison of liposomal irinotecan+5-FU/LV versus 5-FU/LV is relevant to the decision problem (n=258). The primary endpoint was OS. The primary analysis was performed using data from the 14 February 2014 data cut (after 305 deaths had occurred).

Results from the primary analysis of 236 patients in the intention-to-treat (ITT) population of the NAPOLI-1 trial [18] showed that median OS was longer for patients in the liposomal irinotecan+5-FU/LV arm than for patients in the 5-FU/LV arm (6.1 months versus 4.2 months). The difference was reported to be statistically significant (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.49 to 0.92, p=0.0122). Median PFS and time to treatment failure (TTF) were longer for patients treated with liposomal irinotecan+5-FU/LV than for patients treated with 5-FU/LV (3.1 months versus 1.5 months, and 2.3 months versus 1.4 months, respectively); these differences were also reported to be statistically significant (HR 0.56; 95% CI 0.41 to 0.75, p=0.0001 and HR 0.60, p=0.0002 respectively).

Nearly all (248 [98.8%] of 251) patients in the safety population of the NAPOLI-1 trial [18] reported a treatment emergent AE. Treatment-related AEs, Grade ≥3 AEs, serious AEs and dose modifications were higher in the liposomal irinotecan+5-FU/LV arm than in the 5-FU/LV arm. For patients treated with liposomal irinotecan+5-FU/LV, the primary reason for dose delay was myelosuppression (e.g. neutropenia). Myelosuppression and gastrointestinal disorders were the main reasons for dose reductions of liposomal irinotecan+5-FU/LV. The primary reasons for discontinuation of treatment with liposomal irinotecan+5-FU/LV were gastrointestinal disorders, and infections and infestations.

Evidence for HRQoL was derived from a subset of patients in the ITT population of the NAPOLI-1 trial [18] who had completed the EORTC-QLC-C30 questionnaire at baseline and on at least one subsequent occasion. The company reported that there were no appreciable changes from baseline after 12 weeks, suggesting there were no negative effects on HRQoL from the trial treatments. A quality adjusted time without symptoms or toxicity (Q-TWiST) analysis was also reported. The company stated that results from this analysis showed that treatment with irinotecan+5-FU/LV resulted in statistically significant and clinically important gains in quality adjusted survival compared with 5-FU/LV.

The company explored the feasibility of conducting a network meta-analysis (NMA) or ITC to compare the effectiveness of treatment with liposomal irinotecan+5-FU/LV with other relevant comparators (e.g. oxaliplatin+5-FU/LV). The company considered a network of evidence formed by 12 of the RCTs included in its systematic review [7-11, 13-19]. Three trials could be linked by a common comparator (5-FU/LV): the NAPOLI-1 trial [18], the CONKO-003 trial [15] and the PANCREOX trial [11]. However, the company stated that the proportional hazards assumptions (that the relative risk of an event is fixed over time) necessary to generate reliable results were violated for both OS (in the NAPOLI-1 trial [18]) and for PFS (in the CONKO-003 trial [15] and the PANCREOX trial [11]). In addition, the company considered that the trials were too heterogeneous in terms of location, intervention (e.g. trials of oxaliplatin+5-FU/LV differed in terms of cumulative dose of 5-FU, use of bolus 5-FU, total dose of oxaliplatin, and overall scheduling of treatment), patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow-up for results to be used in an ITC. These limitations led the company to conclude that conducting an ITC to generate evidence for clinical effectiveness was “unfeasible”.

## 3.2 Critique of the Clinical Evidence and Interpretation

The ERG considered the NAPOLI-1 trial [18] to be of reasonable quality; however, the ERG noted a risk of bias due to the open-label design. The ERG suggested that this may have been a key factor leading to a greater proportion of patients withdrawing from the 5-FU/LV arm (10.9%) before commencing treatment than from the liposomal irinotecan+5-FU/LV arm (1.7%). The open-label nature of the trial, combined with a lack of independent assessment of disease progression, may also have introduced bias into the assessment of disease progression. The ERG recognised that blinding of study treatment was not feasible due to different dosing schedules for the trial arms.

Generally, clinical advice to the ERG was that the population in the NAPOLI-1 trial [18] was similar to the population considered for treatment with liposomal irinotecan+5-FU/LV in the UK. The main caveat was that, as is often the case with clinical trials, the trial population may have been younger and fitter than the population seen in NHS clinical practice.

The ERG found that the assumptions of proportional hazards for OS, PFS and TTF were not supported in the NAPOLI-1 trial [18]. Therefore, the log-rank test results (hazard ratios and p-values) that the company used to demonstrate statistical significance are not valid. The ERG generally agreed with the company’s overall assessment that the safety profiles of liposomal irinotecan+5-FU/LV were consistent with clinical experience of using liposomal irinotecan in a phase II non-randomized RCT [20]. However, the ERG questioned the robustness of the HRQoL results derived from the EORTC-QLQ-C30 questionnaire given the relatively small number of patient responses over time. In addition, the ERG cautioned that the Q-TWiST analysis had not been presented in the NAPOLI-1 trial [18] Clinical Study Report (CSR) so appeared to be a post-hoc exploratory analysis.

The ERG agreed with the company that there were methodological issues precluding the conduct of an ITC. There was therefore no evidence available to enable a credible comparison between liposomal irinotecan+5-FU/LV and any relevant comparator.

In the absence of results from a credible ITC, the ERG conducted its own crude comparison of efficacy across four RCTs identified in the company’s systematic review that included oxaliplatin+5-FU regimens (i.e. the CONKO-003 [15], PANCREOX [11], SWOG S1115 [10] and Yoo et al [19] trials). As noted by the company, the interventions varied in terms of cumulative dose of 5-FU, use of bolus 5-FU, total dose of oxaliplatin, and overall scheduling of treatment. For patients treated with oxaliplatin+5-FU/LV reported in three trials [10, 11, 15], median OS (ranging from 5.9 to 6.7 months) and PFS (ranging from 2.0 to 3.1 months) were similar to those reported for patients who were treated with liposomal irinotecan+5-FU/LV in the NAPOLI-1 trial [18]. In the fourth trial (Yoo et al [19]), median OS and median PFS reported for patients treated with oxaliplatin+5-FU (3.4 and 1.4 months respectively) were shorter than in the other trials of oxaliplatin+5-FU [10, 11, 15]. In the trial by Yoo et al [19], the comparator arm was non-liposomal irinotecan in combination with 5-FU/LV. The ERG noted that median OS and median PFS were similar for patients treated with non-liposomal irinotecan in combination with 5-FU/LV (3.8 and 1.9 months respectively) to those treated with oxaliplatin+5-FU. The ERG further noted that in the PANCREOX trial [11], median OS of 9.9 months reported in the 5-FU/LV arm is markedly greater than median OS reported for patients in either the oxaliplatin+5-FU/LV or comparator arms of the other four trials (which ranged from 3.3 to 6.7 months) [10, 11, 15, 19]. The ERG concluded that the findings from its crude comparison should only be considered exploratory and treated with caution because of potentially important differences in trial and patient characteristics.

## 3.3 Cost-effectiveness evidence

The company carried out a literature review to identify relevant cost-effectiveness studies. None were identified. The company also developed a de novo economic model to allow the cost-effectiveness of treatment with liposomal irinotecan+5-FU/LV to be compared with 5-FU/LV (company base case) and oxaliplatin+5-FU/LV (NHS standard care). The model comprised four mutually exclusive health states: pre-progression on treatment, pre-progression off treatment, post-progression treatment (including patients receiving second-line therapy and those receiving palliative care) and death. The proportion of patients in the pre-progression on treatment health state was estimated as the difference between PFS and TTF. The proportion of patients in the post-progression treatment state was estimated as the difference between OS and PFS. All patients entered the model in the pre-progression on treatment health state. The model was developed in Microsoft Excel using a 1-week cycle length and a time horizon of 10 years. As recommended by NICE, a discount rate of 3.5% was used for both costs and outcomes, and outcomes were measured in QALYs. The model perspective was that of the NHS. The following costs were included in the model: costs of the intervention and comparator drugs, administration costs, treatment-related monitoring costs, costs for treating AEs, post-progression treatment costs and palliative and terminal care costs. Costs were valued at 2014-15 prices.

Survival for patients treated with liposomal irinotecan+5-FU/LV and patients treated with 5-FU/LV was estimated based on data from the NAPOLI-1 trial [18]. In the base case, log-normal distributions were selected to model OS, PFS and TTF for both treatment arms. Survival for patients treated with oxaliplatin+5-FU/LV utilised data from the company’s ITC. Modelling OS, PFS and TTF in both treatment arms was carried out by using the hazard ratios derived from the company’s ITC to adjust the liposomal irinotecan+5-FU/LV (log-normal) curves to represent the experience of patients treated with oxaliplatin+5-FU/LV. Resource use and costs were estimated based on information from the NAPOLI-1 trial [18], published sources [21-23] and clinical experts. Utility values were expressed in EuroQol-5 dimension (EQ-5D) utility values based on those used in a previous NICE STA of patients with previously untreated metastatic pancreatic cancer [24].

Prior to the first AC meeting, the company agreed a patient access scheme (PAS) with the Department of Health. The scheme provides a simple discount to the list price of liposomal irinotecan+5-FU/LV with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence (CiC) and, therefore, results from analyses using this price cannot be reported here. Using the discounted price, the company’s base case ICER per QALY gained for the comparison of cost-effectiveness of treatment with liposomal irinotecan+5-FU/LV versus 5-FU/LV was £96,591, and for liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV was £54,412.

## 3.4 Critique of the Cost-effectiveness Evidence and Interpretation

The ERG considered oxaliplatin+5-FU/LV (rather than 5-FU/LV) to be the main comparator to liposomal irinotecan+5-FU/LV since 5-FU/LV alone is not used in the NHS to treat the population under consideration. Despite noting that the company’s economic model is structured appropriately according to conventional practice, the ERG identified a number of areas of concern with how the model was implemented.

The first area of concern was related to the company’s methods for modelling survival. Regarding the company’s base case comparison of liposomal irinotecan+5-FU/LV with 5-FU/LV, the ERG noted that almost all of the NAPOLI-1 trial [18] data are complete so that in only one instance is there any need to extrapolate beyond the reported data (involving a single patient still at risk at data cut-off). Furthermore, a biological rationale or justification for selecting log-normal distributions to project survival was not provided by the company. The ERG noted that log-normal models are invariably problematic as they generally lead to overestimates of survival due to their distinctively long tails. Therefore, the ERG considered that was little or no value in fitting parametric survival functions to the trial data. The ERG considered that the original trial data should be used directly, as observed trial data should take precedence over any theoretical mathematical construct.

In relation to the comparison of the cost-effectiveness of treatment with liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV, as highlighted in the critique of clinical effectiveness evidence (see section 3.2), the ERG was concerned that the ITC was so flawed that it could not produce credible results. Therefore, any cost-effectiveness results relating to using ITC results should be viewed with caution. In addition to the limitations of the results from the company’s ITC, the ERG considered, on theoretical grounds, that the company’s use of hazard ratios was inappropriate. The ERG’s conclusion was based on the fact that the company used log-normal curves to project survival and pre-progression on treatment for patients treated with liposomal irinotecan+5-FU/LV. Log-normal models are accelerated failure time models but accelerated failure time distributions do not produce a single hazard ratio [25] and so are incompatible with the proportional hazards assumption. The ERG also noted that an alternative time ratio adjustment could not be performed because the accelerated failure time adjustment criterion was also violated when examining the NAPOLI-1 trial [18] data.

The ERG highlighted that the company’s approach to modelling time on treatment using log-normal parametric curves systematically under-estimated the observed overall time on treatment for patients in both arms of the NAPOLI-1 trial [18]. Time on treatment in the 5-FU/LV arm was found by the ERG to be underestimated by 15%, and in the liposomal irinotecan+5-FU/LV arm by 1.4%. For the comparison of liposomal irinotecan+5-FU/LV with oxaliplatin+5-FU/LV, it was assumed that the pre-progression time on treatment for oxaliplatin+5-FU/LV is equivalent to liposomal irinotecan+5-FU/LV. However, this assumption resulted in the proportion of patients on treatment in the pre-progression on treatment state exceeding the proportion of patients in the PFS state. Therefore, the company employed a model correction to resolve this issue. The ERG considered that the need for a model correction suggested that the company’s approach to modelling time of treatment had been misconceived.

The ERG also identified six issues relating to drug costing. First, the ERG disagreed with the company’s use of pro-rata reductions to drug costs to account for possible wastage, the assumption being that a reduced or missed dose due to AEs also reduced drug acquisition costs. The ERG highlighted that while doctors typically see patients on the same day that treatment is prepared by the pharmacy department, it can be difficult to anticipate the need for treatment alterations in routine clinical practice and notify pharmacy in time to stop or amend drug preparation, especially in NHS centres treating small numbers of patients. Second, the company based costs relevant to dosing on body surface area (BSA) using a value for BSA that was undifferentiated by tumour type or site, and which did not take into account the male: female balance of patients participating in the NAPOLI-1 trial [18]. Third, company drug acquisition costs were substantially overestimated as the costs of purchasing generic drugs were sourced from the British National Formulary [22] rather than NHS sources. Fourth, the model did not incorporate the economic efficiencies that are achievable by using a mixture of different vial sizes. Information in the Department of Health’s electronic market information tool (eMit) database shows that there are multiple vial sizes for each of the generic drugs considered within this appraisal and that, generally, the larger the vial, the lower the cost per unit of the drug [26]. Fifth, following the failure of second-line treatment, the company assumed that patients are likely to receive further chemotherapy, whereas clinical advice to the ERG was that in the NHS, such patients are unlikely to receive further chemotherapy. Sixth, the ERG had concerns about the approach taken to determine the cost of treating a patient with Grade 3 to 4 diarrhoea, namely using a weighted average of day case costs [23]. Since the definition of Grade 3 or higher AEs is that such AEs require hospital admission [27], the ERG considered that using the weighted average of costs for all types of admission [23], rather than just day cases, would be more reflective of the costs to the NHS.

Other important issues identified by the ERG related to the health state utility values used in the model, which were based on those used for the appraisal of nab-paclitaxel in combination with gemcitabine (TA360) [28]. This was a first-line patient population and, therefore, the ERG considered these utility values were likely to overstate HRQoL when applied to a second-line patient population. Moreover, these utility values accounted for treatment-related AEs arising from active chemotherapy. The separate addition, by the company, of disutility values associated with AEs resulted in double counting of treatment related disutility. While the company’s model included disutility for AEs, it excluded the effects of terminal disutility on HRQoL. The ERG considered these effects should have been accounted for in the company’s model.

Given the above important issues, the ERG implemented the following modifications to the company model:

* For the comparison of liposomal irinotecan+5-FU/LV versus 5-FU/LV, Kaplan-Meier data from the NAPOLI-1 trial [18] were used to model OS, PFS and TTF.
* To circumvent the need for the company’s arbitrary model correction for time on treatment for the comparison of liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV, the ERG assumed the time on treatment of oxaliplatin+5-FU/LV to be equal to that of 5-FU/LV.
* For the comparison of liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV and for the comparison of liposomal irinotecan+5-FU/LV versus 5-FU/LV:
  + The ERG applied the full costs for drug acquisition rather than pro-rata costs.
  + The ERG identified specific mean BSA values for patients with upper gastrointestinal cancer [21] and used these to generate weighted acquisition costs for all drugs dosed by BSA.
  + The ERG applied the average prices paid by NHS hospitals in England for generic drugs using data from the eMit database [26] and re-calculated the average cost per dose of the intervention and the comparators to take into account differential vial sizes available.
  + On disease progression, palliative care costs [23] were incorporated into the model by the ERG instead of the costs of additional chemotherapy.
  + For costing AEs, the ERG applied the weighted average of Reference Costs for all types of hospital admission as opposed to the weighted average of day case costs [23].
  + The ERG noted that in the phase III RAINBOW trial [29] of locally advanced or metastatic gastric cancer patients receiving second-line combination chemotherapy had similar demographic characteristics to those in the NAPOLI-1 trial [18]. The ERG, therefore, carried out an analysis using utility values estimated from data from this trial [29] in the company model.
  + The ERG estimated the mean EQ-5D utility during the 4 weeks before death from a study of patients receiving palliative care for advanced lung cancer by Van den Hout et al [30]. To the ERG’s knowledge, this is the only study available presenting utility data derived from patients who are only receiving palliative care for advanced cancer.

Overall, applying all the ERG’s preferred amendments to the company model increased the company’s ICERs per QALY gained for both the comparison of liposomal irinotecan+5-FU/LV versus 5-FU/LV and liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV. Using PAS prices, the increases in the ICERs per QALY gained were from £96,591 to £162,887 and from £54,412 to £106,898, respectively.

Given that the ERG did not consider the results from the company’s ITC to be reliable, and the other issues relating to the company’s approach to modelling survival, the ERG conducted exploratory scenario analyses to compare the cost-effectiveness of liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV under the assumption that, over the model time horizon, treatment with oxaliplatin+5-FU/LV resulted in 10% more, 10% fewer or an equal number of QALYs to treatment with liposomal irinotecan+5-FU/LV. Scenarios resulted in ICERs per QALY gained that ranged from £129,162 or £201,019 (using the company’s base case or ERG modified models, respectively) when the total QALYs for oxaliplatin+5-FU/LV were 10% less than liposomal irinotecan+5-FU/LV to liposomal irinotecan+5-FU/LV being dominated (that is, less effective and more expensive than oxaliplatin+5-FU/LV) when the total QALYs for oxaliplatin+5-FU/LV were 10% more than for liposomal irinotecan+5-FU/LV.

## 3.5 Conclusions of the ERG report

The ERG considered that treatment with liposomal irinotecan+5-FU/LV is of greater efficacy than 5-FU/LV for patients with metastatic pancreatic cancer that has progressed on treatment with gemcitabine. Despite an increase in myelosuppression and gastrointestinal disorders, treatment-related AEs, Grade ≥3 AEs and dose modifications arising from AEs, there was no apparent deterioration in HRQoL when treatment with liposomal irinotecan+5-FU/LV was compared with 5-FU/LV. However, 5-FU/LV is rarely used to treat such patients in NHS clinical practice and it is impossible to say whether liposomal irinotecan+5-FU/LV is more, or less, clinically effective than oxaliplatin+5-FU/LV, oxaliplatin+capecitabine or capecitabine monotherapy.

The ERG considered that the company’s base case cost-effectiveness results for the comparison of liposomal irinotecan+5-FU/LV versus oxaliplatin-5-FU/LV are underestimates and should be interpreted with extreme caution. The ERG identified many modelling issues that affected the cost-effectiveness of the intervention and both comparators. These related to the projection of survival, the drug costing methodologies and the estimation of HRQoL

# 4. Key methodological concerns

There was no head-to-head evidence comparing the effectiveness of treatment with liposomal irinotecan+5-FU/LV versus treatment with oxaliplatin+5-FU/LV in the population of interest. Results from a trial that compared these two treatments would have decreased much of the uncertainty about the relative effectiveness of these treatments.

Another limitation was the unreliability of the reported hazard ratios, a measure of comparative effectiveness of two drugs. The fundamental assumption supporting the mathematics that is generally used to generate hazard ratios is that the event hazards remain proportional over time. In the current appraisal, the ERG’s examination of the Kaplan-Meier data from the NAPOLI-1 trial [18] indicates that this assumption does not hold for OS or PFS. This renders the hazard ratio figures for these two outcome measures meaningless. Furthermore, the ITC mathematics used to generate measures of relative efficacy relies on hazards for each outcome measure being proportional, both within and between, included trials. Analyses carried out by the ERG show that this assumption is not valid and, therefore, the use of ITC results to generate model survival estimates was inappropriate.

# 5. National Institute for Health and Care Excellence Guidance

The AC reviewed the available clinical and cost-effectiveness evidence relating to treatment with liposomal irinotecan+5-FU/LV supplied by the company, as well as testimony from clinical experts and patient representatives.

## 5.1 Consideration of unmet need and most appropriate comparator

The AC heard from a clinical expert that capecitabine monotherapy is sometimes used in England but that 5-FU/LV is rarely used. The AC agreed with the clinical expert’s view, which was in line with that expressed in the company’s submission and ERG report, that the most appropriate comparator to liposomal irinotecan+5-FU/LV in NHS clinical practice was oxaliplatin+5-FU/LV.

The AC also heard from clinical and patient experts that patients with metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine have a poor prognosis and there are few treatments available. The AC heard from patient experts that receiving a diagnosis of metastatic adenocarcinoma of the pancreas is devastating and that symptoms such as weight loss, pain, depression and anxiety can be debilitating and difficult to manage. The AC recognised the desire for an additional treatment option, in light of the poor prognosis for patients with metastatic adenocarcinoma of the pancreas, and the limited range of treatment options available.

## 5.2 Consideration of the evidence for clinical effectiveness

The AC acknowledged the problems with conducting an ITC that were highlighted by both the company and the ERG, although it heard from the company that the company considered that the proportional hazards assumption held for OS up to 21 months in the NAPOLI-1 trial [18], at which point the Kaplan–Meier curves crossed. The AC also heard from the clinical expert that while oxaliplatin+5-FU/LV would be more effective than 5-FU/LV (as reported in the CONKO-003 trial [15] but contrary to the findings reported in the PANCREOX trial [11]), its relative effectiveness compared with liposomal irinotecan+5-FU/LV is difficult to estimate. The AC concluded that the company’s hazard ratios could not be considered reliable for comparing the relative treatment effect of liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV. Acknowledging the ERG’s crude comparison of efficacy data from the NAPOLI-1 trial [18] and results from trials of oxaliplatin+5-FU/LV [10, 11, 15, 19], the AC concluded that the clinical effectiveness of liposomal irinotecan+5-FU/LV could be considered broadly similar to that of oxaliplatin+5-FU/LV.

## 5.3 Consideration of the evidence for cost-effectiveness

While the AC accepted the basic structure of the company's economic model and concluded that it was appropriate to use for decision-making, it shared the ERG’s concerns about the way in which the company had modelled OS, PFS and time on treatment. The AC concluded that because complete data were available for PFS and for time on treatment, and virtually complete data were available for OS, using the Kaplan–Meier data from the NAPOLI-1 trial [18] was more appropriate than extrapolating data using parametric models.

The AC 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. Thus, while planned treatment variations in drug dose can be accounted for when treatment is given, they are difficult to predict in advance. Therefore, the AC concluded that full costing should be assumed in the base case. The AC also concluded that it was inappropriate to assume use of the smallest sized vials and that the ERG’s method of calculating drug acquisition costs was more appropriate than that employed by the company.

The AC heard that the utility values used by the company were considered by the ERG to overestimate HRQoL since they were derived from a study of patients receiving first-line treatment for advanced pancreatic cancer. The company stated that they had chosen to use values from a first-line study [31] because patients in the NAPOLI-1 trial [18] were fitter than those generally considered for second-line treatment in clinical practice and because the baseline performance status scores were similar in the two trials. It was also noted that the values preferred by the ERG came from a study of gastric cancer [29], and the clinical expert cautioned that the population with gastric cancer may not be comparable with people with pancreatic cancer. Therefore, the AC concluded that although there was uncertainty about the most appropriate utility values to use for a second-line treatment population with metastatic pancreatic cancer, the values used by the company were acceptable for decision-making.

The AC noted that the company’s base case ICER per QALY gained for the comparison of the cost-effectiveness of treatment with liposomal irinotecan+5-FU/LV versus 5-FU/LV (which is not established practice in the NHS) was £96,591. However, the AC concluded that the most plausible ICERs would be those generated by the company’s model with all of the ERG’s suggested modifications except the change to utility values. ICERs were available for (i) all ERG modifications (including ERG preferred utility values) and (ii) ERG modifications to survival (as preferred by the AC) with the remaining assumptions taken from the company’s analyses. The ICERs per QALY gained were (i) £162,887 and (ii) £137,354. The ICER was therefore considered by the AC to be more than £100,000 per QALY gained for the comparison of liposomal irinotecan+5-FU/LV with 5-FU/LV.

For the comparison of liposomal irinotecan+5-FU/LV with oxaliplatin+5-FU/LV (standard NHS practice), the AC noted the company’s base case ICER per QALY gained was £54,412. Given the total QALYs, reported in the company submission, for patients receiving oxaliplatin+5-FU/LV were lower than for those receiving 5-FU/LV, which the AC considered to be clinically implausible, the AC also considered results from the ERG’s exploratory analyses which included altering the QALY difference between liposomal irinotecan+5-FU/LV and oxaliplatin+5-FU/LV by +/- 10%. When the total QALYs for oxaliplatin+5-FU/LV were 10% less than for liposomal irinotecan+5-FU/LV, the ICER per QALY gained was £201,019 (using all ERG modifications to the model). When the total QALYs for oxaliplatin+5-FU/LV were 10% more than for liposomal irinotecan+5-FU/LV, treatment with liposomal irinotecan+5-FU/LV was dominated by oxaliplatin+5-FU/LV (whether using the company base case or modified ERG model). The AC concluded that although the analyses comparing the cost-effectiveness of liposomal irinotecan+5-FU/LV with oxaliplatin+5-FU/LV were subject to considerable uncertainty, treatment with liposomal irinotecan+5-FU/LV could not be considered a cost-effective use of NHS resources.

In addition to the ICERs per QALY gained, the AC considered whether there were additional gains in HRQoL not captured by the QALY calculations and concluded that there were none.

## 5.4 End-of-life considerations

The AC also considered whether liposomal irinotecan+5-FU/LV met NICE’s ‘End-of-life’ criteria [32]. The AC accepted that the treatment is indicated for patients with a short life expectancy, normally less than 24 months. Thus, the criterion for short life expectancy was met. However, it was noted that neither the company nor ERG could produce a reliable estimate of the difference in OS between liposomal irinotecan+5-FU/LV and oxaliplatin+5-FU/LV. The AC concluded that the ‘End-of-life’ criteria were not met since there was insufficient evidence that liposomal irinotecan+5-FU/LV offered an extension to life of at least an additional 3 months compared to current NHS treatment.

## 5.5 Final guidance

The FAD was published following the second AC meeting. At this meeting, the AC considered the comments received in response to the Appraisal Consultation Document. Guidance was published on 26 April 2017: liposomal irinotecan was not recommended within its marketing authorization for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy.

# 6. Conclusion

The key clinical and cost-effectiveness issues in this appraisal arose from the difficulty in comparing treatment with liposomal irinotecan+5-FU/LV versus a comparator treatment used routinely in NHS clinical practice. This was primarily because of the lack of a head-to-head trial comparing treatment with liposomal irinotecan+5-FU/LV with a relevant comparator and because methodological weaknesses precluded the conduct of an ITC capable of producing robust and credible results.

The ERG’s primary reason for rejecting the validity of the results from the company’s ITC related to the proportional hazards assumptions being violated both within and between included trials. The ERG also considered that trial heterogeneity was a limitation. The company acknowledged both of these limitations. Due to an absence of reliable ITC results, the ERG undertook a crude treatment effectiveness comparison. The ERG, however, acknowledged that such naïve comparisons have major limitations, and statistical methods to derive ITC results are usually preferable.

Despite making modifications to the company’s economic model and generating estimates for the ICER per QALY gained for a comparison of the cost-effectiveness of liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV, the ERG considers the ICERs per QALY gained generated by its modifications to be only exploratory. Primarily, this is because all of the estimates depend on clinical effectiveness evidence that, for the comparison of liposomal irinotecan+5-FU/LV with oxaliplatin+5-FU/LV is not considered to be sufficiently robust.

Notwithstanding these uncertainties, the AC noted that the company’s base case ICER per QALY gained for the comparison of the cost-effectiveness of treatment with liposomal irinotecan+5-FU/LV versus oxaliplatin+5-FU/LV was more than £50,000, as were the ICERs generated by the ERG’s exploratory analyses. Therefore, despite liposomal irinotecan+5-FU/LV being considered at a confidential discounted price in the current appraisal, the AC was confident that the ICER per QALY gained was more than £50,000 and thus could not be considered a cost-effective use of NHS resources.

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# Contributions of authors:

Nigel Fleeman: Project lead, drafted clinical results section and supervised the final report

Ahmed Abdulla: Critique of the company economic model and proposal of alternative interpretations of the economic evidence

Adrian Bagust: Checking, critique and validation of the economic model/evidence

Sophie Beale: Critical appraisal of the clinical and economic evidence and editorial input

Marty Richardson: Critical appraisal of the statistical evidence

Angela Stainthorpe: Summary and critical appraisal of economic evidence

Angela Boland: Critical appraisal of the clinical and economic evidence and editorial input

Eleanor Kotas: Critical appraisal of the database searching

Joanne McEntee: Critical appraisal of the submission

Daniel Palmer: Clinical advice and critical appraisal of the clinical sections of the company’s submission

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# Compliance with Ethical standards

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## Competing interests

Within the last 3 years Daniel Palmer has received consultancy fees and funds for research from Baxalta, which is now part of Shire Pharmaceuticals. None of the other authors (Nigel Fleeman, Ahmed Abdulla, Adrian Bagust, Sophie Beale, Marty Richardson, Angela Stainthorpe, Angela Boland, Eleanor Kotas, Joanne McEntee) have any competing interests.

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