Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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liposomal irinotecan hydrochloride trihydrate (as irinotecan sucrosofate salt), 5mg/mL concentrate for solution for infusion (Onivyde®) SMC No. (1217/17)

Shire

10 February 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan and end of life process

liposomal irinotecan (Onivyde®) is not recommended for use within NHS Scotland.

Indication under review: Treatment of metastatic adenocarcinoma of the pancreas, in combination with fluorouracil (5-FU) and leucovorin (folinic acid), in adult patients who have progressed following gemcitabine based therapy.

The addition of liposomal irinotecan to 5-FU/folinic acid, compared with 5-FU/folinic acid alone, significantly improved overall survival and progression free survival in patients with metastatic adenocarcinoma of the pancreas who had progressed after gemcitabine based therapy.

The submitting company's justification of the treatment's costs in relation to its health benefits was not sufficient and in addition did not present a sufficiently robust clinical or economic case to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman Designate,
Scottish Medicines Consortium

Indication

Treatment of metastatic adenocarcinoma of the pancreas, in combination with fluorouracil (5-FU) and leucovorin (folinic acid), in adult patients who have progressed following gemcitabine based therapy. [1]

In this document fluorouracil is hereafter referred to as 5-FU and leucovorin is referred to as folinic acid.

Dosing Information

The recommended dose of liposomal irinotecan hydrochloride trihydrate (as irinotecan sucrosofate salt), is 80mg/m^2 intravenously over 90 minutes, followed by folinic acid 400mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400mg/m^2 intravenously over 46 hours, administered every two weeks.

A reduced starting dose of 60mg/m^2 liposomal irinotecan hydrochloride trihydrate should be considered for patients known to be homozygous for the UGT1A1*28 allele. A dose increase to 80mg/m^2 should be considered if tolerated in subsequent cycles.

It is recommended that patients receive pre-medication with standard doses of dexamethasone (or an equivalent corticosteroid) together with a 5-HT3 antagonist (or other antiemetic) at least 30 minutes prior to liposomal irinotecan infusion.[1]

Liposomal irinotecan hydrochloride trihydrate must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti-cancer therapies. It is not equivalent to non-liposomal irinotecan formulations and should not be interchanged.

Product availability date

Anticipated in December 2016.
Liposomal irinotecan meets SMC orphan and end of life criteria.

Summary of evidence on comparative efficacy

Irinotecan (and its more potent active metabolite SN-38) is a specific, reversible inhibitor of the enzyme DNA topoisomerase 1. In the pegylated liposomal formulation, irinotecan free base is encapsulated in lipid bilayer vesicles (liposome nanoparticles). The aim is to increase the time that irinotecan remains in the blood, by protecting it from conversion to SN-38, thereby increasing the concentration and duration of both irinotecan and SN-38 inside the tumour.[3, 4] Liposomal irinotecan hydrochloride trihydrate (hereafter referred to as liposomal irinotecan) in combination with 5-FU/folinic acid, is the first licensed treatment available for patients with metastatic adenocarcinoma of the pancreas who have progressed after gemcitabine treatment.

The evidence supporting the marketing authorisation is from a phase III, randomised, open-label study, NAPOLI-1, that recruited adult patients with histologically or cytologically confirmed pancreatic ductal adenocarcinoma and documented distant metastatic disease. Eligible patients had disease progression following previous gemcitabine based treatment in one of the following settings: neoadjuvant, adjuvant (only if distant metastases occurred within six months of completing adjuvant therapy), locally advanced, or metastatic. They were also required to have a Karnofsky performance status score ≥70 and adequate

haematological, hepatic and renal function. Patients could have previously received irinotecan or 5-FU or both.[3]

The initial protocol randomised patients equally to one of two arms: liposomal irinotecan monotherapy or 5-FU/folinic acid. After a protocol amendment allowed a third combination treatment arm, patients were then randomised in a 1:1:1 ratio to receive treatment until disease progression or intolerable toxic effects, with one of the following:

- liposomal irinotecan (80mg/m^2 intravenous [IV] infusion over 90 minutes) plus 5-FU/folinic acid (400mg/m^2 folinic acid IV infusion over 30 minutes followed by 2400mg/m^2 5-FU IV infusion over 46 hours) every two weeks (n=117)
- liposomal irinotecan monotherapy (120mg/m^2 IV infusion) every three weeks; (n=151)
- 5-FU/folinic acid alone (200mg/m^2 folinic acid IV infusion over 30 minutes followed by 2000mg/m^2 5-FU IV infusion over 24 hours) every week for the first four weeks of each 6-week cycle (n=149: full study and n=119).[3]

Randomisation was stratified by baseline albumin levels (≥40g/L; <40g/L), Karnofsky performance status (70 and 80; ≥90), and ethnic origin (white; east Asian; all others).[3] All patients underwent *UGT1A1* genotype testing and those found to be homozygous for the *UGT1A1*28* allele (n=7 in both the liposomal irinotecan combination and monotherapy arms) received a reduced (by 20mg/m^2) initial dose of liposomal irinotecan (60mg/m^2 in the combination arm and 100mg/m^2 in the monotherapy arm). The doses were increased to the standard dose after the first cycle unless there were adverse effects.[3] Thirty-five per cent (41/117) of patients receiving liposomal irinotecan plus 5-FU/folinic acid had a treatment duration of at least 18 weeks compared with 15% (16/105) of patients receiving 5-FU/folinic acid alone.[4] Post-progression, anticancer therapy was received by 31% (36/117) of patients who had received liposomal irinotecan plus 5-FU/folinic acid and 38% (45/119) of patients who had received 5-FU/folinic acid and was reported as generally similar between treatment groups. In eight and nine patients in the respective groups, post-progression treatment included irinotecan.[3]

The primary outcome, overall survival (OS) was planned to be analysed in the intention to treat population (all randomised patients) after at least 305 patients had died across all treatment groups. At the cut-off date, February 2014, a total of 313 patients had died.[3] Results are presented in this document for the liposomal irinotecan plus 5-FU/folinic acid combination arm and its comparator 5-FU/folinic acid (n=119) arm only, as liposomal irinotecan monotherapy is unlicensed. After a median treatment exposure of 8.7 weeks for liposomal irinotecan plus 5-FU/folinic acid and 6.0 weeks for 5-FU/folinic acid, there was a significant increase in median OS in patients receiving liposomal irinotecan plus 5-FU/folinic acid (n=117) compared with 5-FU/folinic acid alone (n=119): 6.1 months versus 4.2 months; hazard ratio (HR) 0.67 (95% CI: 0.49 to 0.92; p=0.012).[3]

Updated OS results are available from a poster presentation at cut-off date May 2015. After 378 patients across all treatment groups had died, median OS was 6.2 months in the liposomal irinotecan plus 5-FU/folinic acid group versus 4.2 months in the 5-FU/folinic acid group; unstratified HR 0.75; p=0.042. However this analysis was descriptive only.[5]

A pre-specified subgroup analysis in 29 patients who had received prior treatment with standard irinotecan indicated a non-significant reduction in OS for the combination of liposomal irinotecan plus 5-FU/folinic acid compared with 5-FU/folinic acid alone. The proportion of patients that had died was 83% (10/12) versus 47% (8/17) deaths; HR 1.25 (95% CI: 0.49 to 3.19).[3]

Median progression-free survival (PFS: defined as time from randomisation to death or disease progression assessed by the investigator according to RECIST v1 criteria), a secondary outcome, was significantly increased in patients receiving liposomal irinotecan plus 5-FU/folinic acid compared with 5-FU/folinic acid alone: 3.1 months versus 1.5 months; unstratified HR 0.56 (95% CI: 0.41 to 0.75,

p=0.0001).[3] Objective response rate (confirmed complete or partial response assessed by the investigator) was significantly higher in the liposomal irinotecan plus 5-FU/folinic acid group than in the 5-FU/folinic acid group: 16% (19/117) versus 0.8% (1/119); respectively; p<0.0001.[3, 4]

Quality of life was assessed using the European Organisation for Research and Treatment Core Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire, however data were available for approximately 60% of patients only. In all treatment arms, there was a healthy level of physical, emotional and cognitive functioning at baseline and no noticeable deterioration during the study. Baseline median Global Health Status, Functional Scale and Symptoms Scale scores were similar among treatment groups. Baseline symptom scores were low. There was no substantive worsening throughout the study in median symptom scores for pain, dyspnoea, insomnia, appetite loss or constipation. There was an increase from baseline in median symptom scores for nausea/vomiting and diarrhoea.[4]

Summary of evidence on comparative safety

Treatment emergent adverse events (TEAE) were reported for 99% (116/117) of patients in the liposomal irinotecan plus 5-FU/folinic acid group and 98% (132/134) of patients in the 5-FU/folinic acid group and these were of at least grade 3 severity in 77% versus 56% of the respective groups. TEAE led to dose reduction in 33% (39/117) versus 3.7% (5/134); and to discontinuation in 11% (13/117) versus 7.5% (10/134) of patients in the respective groups. Serious TEAE were reported in 48% (56/117) of patients in the liposomal irinotecan plus 5-FU/folinic acid group and in 45% (60/134) of patients in the 5-FU/folinic acid group.[3,4] Treatment-related adverse effects were reported in 92% (107/117) and 69% (93/134) of patients respectively.[4]

Common TEAE in patients receiving liposomal irinotecan plus 5-FU/folinic acid compared with 5-FU/folinic acid were: diarrhoea (59% [≥grade 3, 13%] versus 26% [4.5%]); vomiting (52% [11%] versus 26% [3.0%]); nausea (51% [7.7%] versus 34% [3.0%]); decreased appetite (44% [4.3%] versus 32% [2.2%]); fatigue (40% [14%] versus 28% [3.7%]); neutropenia (39% [27%] versus 5.2% [1.5%]); anaemia (38% [9.4%] versus 23% [6.7%]); hypokalaemia 12% [3.4%] versus 8.9% [2.2%]); alopecia (14% versus 4.5%).[3]One death (due to septic shock) in the liposomal irinotecan combination group was considered to be treatment-related. [3]

Thromboembolic events were reported in up to 6% of patients in the liposomal irinotecan combination arm. In other clinical studies with liposomal irinotecan, deep vein thrombosis, pulmonary embolism, and embolism were considered common adverse events. [4]

Long-term safety data are very limited as only eight patients have received liposomal irinotecan for more than one year.[4] However, safety information is available from the standard formulation of irinotecan.

Summary of clinical effectiveness issues

In 2013 approximately 9,400 new cases of pancreatic cancer were diagnosed in the UK, an increase of 10% over the previous decade.[6] Most (85% to 95%) pancreatic cancers are adenocarcinomas. Late diagnosis is typical; less than half of all pancreatic tumours are diagnosed before metastasis and only 15 to 20% are operable.[4] First-line treatments for patients with locally advanced or metastatic pancreatic ductal adenocarcinoma include FOLFIRINOX (combination of oxaliplatin, folinic acid, irinotecan, and 5-FU) or paclitaxel albumin in combination with gemcitabine.[3] Clinical experts consulted by SMC have advised that most patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine based therapy receive best supportive care (BSC) as they are not fit enough for further chemotherapy. In patients with good performance status, the predominant treatment is a

combination of oxaliplatin plus 5-FU/folinic acid or oxaliplatin plus capecitabine with a median overall survival estimate of six months.[7,8] There are no standard treatments after gemcitabine failure and therefore there is no key comparator and the evidence base is weak for all options. Liposomal irinotecan is the first licensed treatment for the indication under review. Liposomal irinotecan meets SMC end of life and orphan criteria.

In NAPOLI-1, the addition of liposomal irinotecan to 5-FU/folinic acid, compared with 5-FU/folinic acid alone, significantly improved OS (by 1.9 months), PFS (by 1.6 months) and objective response rate (16% versus 1%) in patients with metastatic adenocarcinoma of the pancreas who had progressed after gemcitabine based (single agent or combination) treatment.[3] Generally the toxicity of liposomal irinotecan was manageable and no unexpected differences from the known safety profile of standard irinotecan have become apparent.[4]

A pre-specified subgroup analysis in the small number of patients (n=29) who had received prior treatment with standard irinotecan demonstrated a numerical reduction in OS for the combination of liposomal irinotecan plus 5-FU/folinic acid compared with 5-FU/folinic acid alone. The European Medicines Agency (EMA) noted that: "This observation is also confirmed by univariate and multivariate analyses conducted to identify possible prognostic factors for both OS and PFS, which consistently showed that prior irinotecan, together with age >65, negatively impacted on the prognosis of patients treated with the combination arm. The lack of benefit (if not a detrimental effect) in patients pre-treated with irinotecan raises concerns due to the increasing use of irinotecan-containing regimen as first line therapy. Due to the limited number of patients with prior exposure to non-liposomal irinotecan, the benefit of liposomal irinotecan has not been established in this population."[4] This may affect generalisability to patients in Scotland if pre-treated with FOLFIRINOX but this is likely to impact on very few patients.

The main limitation of the pivotal study is that the comparator is not used in Scotland for the indication under review. In addition, all patients in the NAPOLI-1 study underwent *UGT1A1* genotype testing and those that were homozygous for the *UGT1A1*28* allele received a reduced initial dose of liposomal irinotecan. Clinical experts consulted by SMC have advised that this testing is not used in Scotland. Therefore patients who are homozygous for the *UGT1A1*28* allele could potentially receive an initial dose of liposomal irinotecan that is too high. Furthermore the dosing regimens of 5-FU/folinic acid in the liposomal irinotecan combination arm and control arm were different, although the EMA considered that the difference was unlikely to be relevant in terms of OS.

The submitting company presented a Bucher adjusted indirect comparison of liposomal irinotecan plus 5-FU/folinic acid with oxaliplatin plus 5-FU/folinic acid in patients with metastatic pancreatic cancer who have failed on gemcitabine based therapy. Three studies were included in the analysis NAPOLI-1, CONKO-003 and PANCREOX and the common control arm was 5-FU/folinic acid.[3,7,8] The key outcomes were OS and PFS. There was no significant difference between liposomal irinotecan plus 5-FU/folinic acid compared with oxaliplatin plus 5-FU/folinic acid for OS and PFS. Limitations of the indirect comparison include heterogeneity in terms of prior gemcitabine treatment (monotherapy/combination), study dose regimens, common control arm outcome results, geographical location, follow-up durations and patient age. The Bucher method does not deal with heterogeneity. Assumptions have been made on several aspects such as dosing schedule and follow-up, which introduces bias and uncertainty. Despite the CONKO-003 and PANCREOX studies having contradictory results, the data were pooled. The submitting company has concluded that the results should be treated with caution and the limitations of the analysis should be considered when assessing these results.

Summary of Patient and Clinician Engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of liposomal irinotecan as an end of life and orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Pancreatic cancer is a devastating disease and the associated symptoms and psychological stress of this diagnosis have a significant impact on the quality of life of both patients and their carers. There are limited options for the treatment of pancreatic cancer in NHS Scotland, resulting in inequity with patients with other types of cancer.

- Liposomal irinotecan, in combination with 5-FU/folinic acid is the only licensed, evidence-based, second-line treatment. It is most likely to be considered in a small number of carefully selected patients who have progressed following gemcitabine doublet chemotherapy and have good performance status.

- The potential to access a further treatment option may offer hope to patients and their families/carers and may relieve the psychological impact of the disease.

- The potential for a two month survival benefit reflects a 50% improvement which is considered clinically important in this context. Patients may be able to care for themselves for longer.

- Although there are tolerability issues with liposomal irinotecan, patients would be carefully selected and adverse events are generally considered to be manageable. Improvements in quality of life may be achievable by treating the cancer symptoms and managing these adverse events.

Additional Patient and Carer Involvement

We received a joint patient group submission from Pancreatic Cancer UK and Pancreatic Cancer Action, both are registered charities. Pancreatic Cancer UK has received less than 1% pharmaceutical company funding in the last two years, including from the submitting company. Pancreatic Cancer Action has received 2.5% pharmaceutical company funding in the past two years but none from the submitting company. Representatives from Pancreatic Cancer UK participated in the PACE meeting. The key points of the joint submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost- utility analysis comparing liposomal irinotecan plus 5-FU/folinic acid to oxaliplatin plus 5-FU/folinic acid, for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine therapy. The time horizon in the model was 10 years. SMC clinical expert responses have indicated that oxaliplatin plus 5-FU/folinic acid appears to be a reasonable comparator.

A partitioned survival model was provided by the company and was used to estimate the proportion of patients in each health state at a given time point. This type of model uses area under the curve (AUC), as opposed to transition probabilities to estimate patient movement within the model. The model contained three primary health states including ‘alive with no progression’, ‘alive with progression’ and

death. In order to account for differences in costs within the pre- progression health state, this was divided into 'pre- progression on treatment' and 'pre- progression off treatment'.

The key clinical parameters used within the economic analysis were OS and PFS. For liposomal irinotecan plus 5-FU/folinic acid, these data were taken from the pivotal study.[3] Patient level data were used to create Kaplan-Meier curves and a log-normal function was fitted to these data. It is worth noting that, according to the March 2016 final cut data, 100% of patients had died. As such the requirement to extrapolate did not appear to be necessary. Based on this analysis, liposomal irinotecan plus 5-FU/folinic acid resulted in mean modelled OS and PFS of 40.8 weeks and 21.9 weeks respectively. In the clinical study these values were reported as 40.8 weeks and 24.7 weeks respectively.

Due to the lack of head to head studies comparing liposomal irinotecan plus 5-FU/folinic acid to oxaliplatin plus 5-FU/folinic acid, comparative clinical efficacy was estimated using the Bucher indirect comparison, by applying the resultant hazard ratios to the modelled Kaplan-Meier estimates referred to above. Based on the results of the indirect comparison, oxaliplatin plus 5-FU/folinic acid resulted in mean OS of 25.7 weeks and mean PFS of 15.3 weeks respectively. Despite crossing OS curves within the pivotal study, the economic analysis assumed that proportional hazards applied.

The key utility values used within the analysis were 0.80 and 0.75 for the pre-progression and post-progression health states respectfully. Values were taken from a US published study, whereby the EQ-5D was used to elicit Health Related Quality of Life (HRQoL) values from patients with advanced pancreatic cancer. Disutilities associated with treatment related adverse events were also included.

Drug acquisition costs, administration costs and monitoring costs were included in the analysis. The cost of treating adverse events were also included and were considered to be equivalent for both treatment arms i.e. £14.17 per week, but the total adverse event costs were higher in the liposomal irinotecan arm due to a longer duration of therapy.

The base case results showed that liposomal irinotecan plus 5-FU/folinic acid resulted in an incremental cost effectiveness ratio (ICER) of £65,922 versus oxaliplatin plus 5-FU/folinic acid, based on an incremental cost of £14,647 and an incremental quality adjusted life year (QALY) gain of 0.2222.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS offered a simple discount on the list price of the medicine. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The company provided one-way, scenario analysis and probabilistic sensitivity analysis. For the scenario analysis, results were most sensitive to the assumption that a proportion of patients (31%) go on to receive further chemotherapy therapy after 2nd line treatment, as per the pivotal study, rather than the base case assumption of all patients receiving only palliative care. Based on this analysis, liposomal irinotecan plus 5-FU/folinic acid resulted in an ICER of £76,320 (without PAS) compared to oxaliplatin plus 5-FU/folinic acid. When alternative utility values were used for the pre- progression and post-progression health states i.e. 0.742 and 0.671 respectively, to account for lower utility values typically being found in UK populations compared to US studies, the ICER increased to £72,816 (without PAS) .

There were a number of weaknesses within the economic analysis. These are as follows;

- The HR estimated for liposomal irinotecan plus 5-FU/folinic acid versus oxaliplatin plus 5-FU/folinic acid (for PFS and OS) is not statistically significantly different. This indicates that there is considerable uncertainty surrounding the additional clinical benefit associated with liposomal

irinotecan plus 5-FU/folinic acid. The company provided an additional sensitivity analysis, where these effects were removed and thus where the analysis would be considered a cost-minimisation analysis. Based on this analysis, where liposomal irinotecan plus 5-FU/folinic acid was associated with no QALY gain, liposomal irinotecan plus 5-FU/folinic acid resulted in an incremental cost of £12,562 (without PAS). This analysis may be particularly conservative as it assumes no additional benefit with liposomal irinotecan plus 5-FU/folinic acid, however there was limited additional sensitivity analysis that varied the level of effectiveness between the base case values (based on non-significant differences) and the cost-minimisation analysis result. A probabilistic sensitivity analysis which had the potential to incorporate variation in the hazard ratios to take account of the uncertainty with the indirect comparison unfortunately produced results which lacked face validity.

- There are no head to head data comparing the efficacy of liposomal irinotecan plus 5-FU/folinic acid to the primary comparator oxaliplatin plus 5-FU/folinic acid. As such relative efficacy is derived from an indirect comparison which contains a number of weaknesses, as described in the clinical effectiveness section above, that further limit the validity of economic results.

- In the economic analysis, the company opted to attach a log-normal parametric function to the Kaplan-Meier data in the pivotal study.[3] This approach may have been unnecessary as the data for OS were mature. The company was asked to comment on why it was deemed appropriate to extrapolate and have subsequently responded indicating that due to a lack of complete Kaplan-Meier data within the oxaliplatin studies, a function was used for liposomal irinotecan plus 5-FU/folinic acid so that a hazard ratio for oxaliplatin could be applied. Based on feedback from the SMC statistical advisor, use of the Kaplan-Meier data appeared to better reflect the reality of the study. Therefore in order to address this uncertainty, the company was asked to provide a revised analysis using the Kaplan-Meier (observed data) only. Based on this analysis, liposomal irinotecan plus 5-FU/folinic acid resulted in an ICER of £74,340 (without PAS) versus oxaliplatin plus 5-FU/folinic acid.

- Considering the nature of the disease, the base case utility values for the pre- progression and post-progression health states appeared quite high. These utilities were previously used and criticised in a review of paclitaxel SMC (968/14). As noted above, the use of values adjusted for a UK population resulted in an increase in the ICER. The submitting company also provided an additional set of analyses that combined both the lower values of quality of life and the use of the Kaplan-Meier data. This resulted in an ICER of £81,488 (without PAS).

The Committee considered the benefits of liposomal irinotecan in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as liposomal irinotecan is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept liposomal irinotecan for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2015. It notes that a randomised study in 168 patients (CONKO-003) has shown, in patients with advanced gemcitabine-refractory pancreatic cancer that second-line 5-FU/folinic acid and oxaliplatin, significantly extend the duration of overall

survival when compared with 5-FU/folinic acid alone. These results have not been confirmed by a more recent Canadian trial (PANCREOX). Very recently, combination of a liposomal encapsulation of irinotecan, and 5-FU/folinic acid has shown an improvement of overall survival (6.1 versus 4.2 months), PFS and objective response rate in the intent-to-treat population over 5-FU/folinic acid alone. Second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the use of oxaliplatin, liposomal irinotecan when available in all countries may be the best option for second-line treatment of these patients.[9]

Additional information: comparators

Oxaliplatin plus 5-FU/folinic acid combination treatment regimens or oxaliplatin plus capecitabine.

Cost of relevant comparators

Drug	Dose Regimen (all medicines administered by intravenous infusion unless stated otherwise)	Cost per cycle (£)
Liposomal irinotecan plus 5-FU/folinic acid	**Liposomal irinotecan 80mg/m^2 plus Folinic acid; 400mg/m^2 plus 5-FU 2400mg/m^2; once every 2-week cycle**	**2,141 / 2 week cycle**
Oxaliplatin plus 5-FU/folinic acid (OFF regimen)	Oxaliplatin 85mg/m^2 on days 8 and 22 plus Folinic acid 200mg/m^2 on days 1, 8, 15, 22 plus 5-FU 2000mg/m^2 on days 1, 8, 15, 22 of a 6-week cycle	2,000 / 6 week cycle
Oxaliplatin plus capecitabine (CapOx)	Oxaliplatin 130mg/m^2 on day 1 plus Capecitabine orally 2g/m^2 daily on days 1 to 14 of a 3-week cycle	1,004 / 3 week cycle
Oxaliplatin plus 5-FU/folinic acid (mFOLFOX6 regimen)	Oxaliplatin 85mg/m^2 plus Folinic acid 400mg/m^2 plus 5-FU 400mg/m^2 bolus then 2400mg/m^2; once every 2-week cycle	928 / 2 week cycle

Doses are for general comparison and do not imply therapeutic equivalence. All costs are from Dictionary of Medicines and Devices (dm&d) except for liposomal irinotecan, from company submission and capecitabine from eVadis on 03.11.16. Costs based on 1.8m^2 body surface area. Treatment with liposomal irinotecan is continued until disease progression or unacceptable toxicity. Median exposure to liposomal irinotecan plus 5-FU/folinic acid in NAPOLI-1 was 8.7 weeks (= 4 complete cycles). CapOx regimen from SMC Clinical expert advice; capecitabine is not licensed for pancreatic cancer.
Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 135 patients eligible for treatment with liposomal irinotecan in all years to which confidential estimates of treatment uptake were applied.

Without PAS

The gross impact on the medicines budget was estimated to be £120k in year 1 rising to £598k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £90k in year 1 rising to £451k in year 5.

The analysis also included savings and additional costs for administration, monitoring, palliative care and adverse events. Taking these into account the net total budget impact was £98k in year 1 rising to £493k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

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5. Wang-Gillam ALCPBGDASYSJGSMTLKHCDBJ. Updated overall survival analysis of NAPOLI-1: Phase III study of nanoliposomal irinotecan (nal-IRI, MM-398), with or without 5-fluorouracil and leucovorin (5-FU/LV), versus 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy.

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7. Gill S, Ko YJ, Cripps MC, Beaudoin A, Dhesy-Thind SK, Zulfiqar M*, et al.* PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients who have received gemcitabine-based chemotherapy.

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9. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D*, et al.* Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.

This assessment is based on data submitted by the applicant company up to and including 14 December 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.