Review of TA440; Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

TA440 was published in April 2017 and scheduled to be considered for review in 2020.

Decision

1. The guidance should be transferred to the 'static guidance list'.

Rationale

2. There is no new evidence to address the key uncertainties identified in the original appraisal. The relative effectiveness of pegylated liposomal irinotecan compared with current practice was highly uncertain in the original appraisal. Head-to-head randomised trial data was needed, or further evidence to inform an indirect treatment comparison. The review did not find evidence to resolve these issues.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

3. No changes have been made to the price of pegylated liposomal irinotecan since the guidance was published.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

4. There are no proposed changes to the marketing authorisation that would affect the existing guidance.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

5. The key uncertainties in the clinical evidence in the original guidance were:

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a. There was no published randomised controlled trial comparing the effectiveness of pegylated liposomal irinotecan with the relevant comparator (oxaliplatin with 5-fluorouracil (5-FU) and leucovorin (LV)).

b. Direct evidence for the clinical effectiveness of pegylated liposomal irinotecan is only available compared with 5-FU plus LV, which is rarely offered to people who have previously had gemcitabine in the NHS (the population in this appraisal).

c. The company and ERG considered it was not possible to derive a credible estimate of clinical or cost-effectiveness for pegylated liposomal irinotecan compared with oxaliplatin with 5-FU plus LV. The trials in the network meta-analysis were too heterogeneous, in terms of trial location, patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow up, to be used in an indirect treatment comparison.

Since the guidance was published, the recommended treatment after gemcitabine has been updated in the American Society of Clinical Oncology metastatic pancreatic cancer clinical guideline[1] to:

- fluorouracil plus pegylated liposomal irinotecan, or
- fluorouracil plus irinotecan when pegylated liposomal irinotecan is not available,

because of conflicting evidence on the efficacy of oxaliplatin. Oxaliplatin with 5-FU plus LV, the key comparator in the original appraisal, is still supported when fluorouracil plus pegylated liposomal irinotecan availability is limited or when residual toxicity from first line therapy or comorbidities precludes the use of fluorouracil plus pegylated liposomal irinotecan. The NICE guideline for pancreatic cancer in adults: diagnosis and management (2018) recommends considering oxaliplatin-based chemotherapy as second-line treatment for people who have not had first-line oxaliplatin.

There are still no completed or ongoing head-to-head randomised controlled trials comparing pegylated liposomal irinotecan with oxaliplatin with 5-FU plus LV. There is no new evidence that would help to inform an indirect treatment

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comparison. There is an ongoing phase 3 randomised controlled trial comparing pegylated liposomal irinotecan with gemcitabine and nab-paclitaxel first line, which is currently recruiting with an estimated primary completion date of December 2022. This may result in an extension to the current licence for pegylated liposomal irinotecan to use as a first line treatment.

During the review proposal process the company highlighted a retrospective study of nanoliposomal irinotecan with 5-FU plus LV compared with oxaliplatin plus fluoropyrimidines, in people with gemcitabine-pretreated metastatic pancreatic adenocarcinoma [2]. The study includes 52 patients treated with nanoliposomal irinotecan with 5-FU plus LV. There was a statistically significant difference in progression-free survival for nanoliposomal irinotecan with 5-FU plus LV compared with oxaliplatin plus fluoropyrimidines, 4.49 months and 3.44 months respectively (p=0.007), but not overall survival. This evidence does not resolve the key uncertainties identified in the original appraisal as it is an observational, uncontrolled study. Further it does not show a difference in overall survival.

The company highlighted a second post-hoc registry analysis for people with locally advanced and metastatic pancreatic cancer[3], but it had a relatively small sample size covering all lines of therapy and may be biased because of earlier switching to second line treatment because of closer monitoring of disease activity. This study does not provide evidence that resolves the clinical uncertainties identified in the original appraisal.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

6. The NICE guideline for pancreatic cancer in adults: diagnosis and management (2018) recommends considering oxaliplatin-based chemotherapy as second-line treatment for people who have not had first-line oxaliplatin. This has no implications for the existing guidance.

Additional comments

7. The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process, MEDLINE Epub Ahead of

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Print, and Embase. References from 21 January 2016 to 20 October 2020 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

Equality issues

No equalities issues were raised during this appraisal.

Proposal paper sign off

Ross Dent – Associate Director, Technology Appraisals and Highly Specialised Technologies

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Contributors to this paper

Information Specialist: Toni Shaw

Technical Analyst: Jessica Cronshaw

Associate Director: Ross Dent

Project Manager: Charlotte Downing

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Appendix A – Information from existing guidance

Original remit

To appraise the clinical and cost effectiveness of nanoliposomal irinotecan within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas after prior treatment with gemcitabine-based treatments.

Current guidance

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.

Research recommendations from original guidance

N/A

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Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be Cross referred into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

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Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

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Appendix C – Other relevant information

Relevant Institute work

Published

Pancreatic cancer in adults: diagnosis and management (2018) NICE guideline NG85

Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine (2017) NICE technology appraisal guidance 440

In progress

Pancreatic cancer - capecitabine. NICE technology appraisal guidance. Publication date to be confirmed. *Suspended June 2019.*

Pancreatic cancer (locally advanced, metastatic) - masitinib. NICE technology appraisal guidance. Publication date to be confirmed. *Suspended July 2014.*

Paclitaxel as albumin-bound nanoparticles with gemcitabine for adjuvant treatment of pancreatic cancer. NICE technology appraisal guidance. Publication date to be confirmed. *Suspended March 2020: "…the company have advised that they are no longer pursuing a Marketing Authorisation Application from the European Medicines Agency for this indication at this time."*

PEGPH20 with nab-paclitaxel and gemcitabine for treating metastatic pancreatic cancer. NICE technology appraisal guidance. Publication date to be confirmed. *Suspended July 2020: "…the company have advised that they are no longer pursuing a Marketing Authorisation Application from the European Medicines Agency for this indication at this time."*

Olaparib for maintenance treatment of BRCA mutation-positive metastatic pancreatic cancer after initial platinum-based chemotherapy. NICE technology appraisal guidance. Publication date to be confirmed. *August 2019: "…following on from advice received from the company, further information regarding the timelines for this appraisal will be available in due course."*

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Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

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.

£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.

Proposed marketing authorisation (for this appraisal) and current price

Current eBNF (accessed 20 Oct 20) gives the same indication: “Metastatic adenocarcinoma of the pancreas in patients who have progressed following gemcitabine based therapy (in combination with fluorouracil and leucovorin) (specialist use only)”.

eBNF lists Onivyde pegylated liposomal 43mg/10ml concentrate for solution for infusion vials (Servier Laboratories Ltd) as costing £615.35 per vial.

Registered and unpublished trials:

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Trial name and registration number	Details
Second-line Therapy With Nal-IRI After Failure Gemcitabine/Nab-paclitaxel in Advanced **Pancreatic Cancer** - Predictive Role of 1st-line Therapy (PREDICT) NCT03468335	"Research hypothesis: Patients profit from 2nd-line therapy with Nal-IRI if they also had a benefit from 1st-line treatment. Benefit from treatment (either 1st or 2nd-line) will be defined as a patient specific Time-To-Treatment Failure (TTF) which is in the upper third of the distribution of TTF values of the studied population." Open label, single arm, multicenter phase IIIb trial. Estimated Study Completion Date: October 31, 2020. No results posted on the trial record.

Additional information

MHRA published safety advice for the use of liposomal irinotecan in March 2019. 'Liposomal irinotecan has been associated with reports of serious thromboembolic events, such as pulmonary embolism, venous thrombosis and arterial thromboembolism. Healthcare professionals are advised to obtain a thorough medical history to identify patients with multiple risk factors. Patients should be advised to seek medical advice immediately if signs or symptoms of thromboembolism occur, such as sudden pain and swelling in a leg or an arm, sudden onset of coughing, chest pain or difficulty breathing.'

References

1. Sohal D, Kennedy E and Khorana A et al. (2018) Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 36 (24): 2545-2556.
2. Kieler M, Unseld M and Bianconi D et al. (2019) A real-world analysis of second-line treatment option in pancreatic cancer: liposomal-irinotecan plus 5-fluorouracil and folinic acid. *Therapeutic Advances in Medical Oncology.* 11: 1-13.
3. Kieler M, Unseld M and Bianconi D et al (2020) Impact of new chemotherapy regimens on the treatment landscape and survival of locally advanced and metastatic pancreatic cancer patients. *Journal of Clinical Medicine.* 9(648).

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