NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA191; Capecitabine for the treatment of advanced gastric cancer

This guidance was issued in July 2010

The review date for this guidance is May 2013

1. Recommendation

TA191 should be transferred to the 'static guidance list'.

That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of capecitabine, within its licensed indication, for the treatment of advanced gastric cancer.

3. Current guidance

1.1 Capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer

4. Rationale[1]

There is no new evidence to suggest that the recommendations of TA191 should change nor any ongoing trials of capecitabine that might be expected lead to a change in the recommendations. There has been no relevant change to the price of capecitabine. It anticipated that generic formulations will be available in the near future.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal'

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from October 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

the ‘Summary of evidence and implications for review’ section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Capecitabine has a marketing authorisation for first-line treatment of advanced gastric cancer in combination with a platinum based regimen. The marketing authorisation for advanced gastric cancer has not changed since the original guidance TA 191 was published.

The patent protection for Xeloda will expire in November 2013, although several generic formulations of capecitabine have now received marketing authorisations for this indication in preparation of the patent expiry. The price of Xeloda is still listed as £40.02 for a 150 mg, 60-tab pack and £265.55 for a 500 mg, 120-tab pack. However, it is expected that the generic capecitabine will be available at cheaper prices once launched in the UK, thereby strengthening the positive recommendation made in TA 191. Fluorouracil (the comparator in TA 191) was available in the generic form at the time of the original guidance and the price has remained the same.

The only other new treatment that could have been considered a likely comparator for capecitabine for treating advanced gastric cancer is tegafur with gimeracil and oteracil (Teysuno, Nordic Group BV), (*Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin*). Tegafur with gimeracil and oteracil is licensed as part of a double regimen with cisplatin, while capecitabine is also used as part of a triple regimen with epirubicin and a platinum compound in current clinical practice. During a scoping exercise for a proposed appraisal of tegafur with gimeracil and oteracil for gastric cancer, clinicians confirmed that double regimens of capecitabine and platinum compounds are only used in clinical practice when there is a specific contraindication to epirubicin. Clinicians did not consider that tegafur with gimeracil and oteracil had clearly demonstrated benefits over capecitabine and the topic was not referred after the scoping workshop.

The evidence in TA 191 was derived from 2 randomised controlled trials evaluating the efficacy of capecitabine compared with fluorouracil in combination with a platinum based drug or as part of a triplet regimen (including a platinum drug). The REAL-2 trial compared epirubicin plus cisplatin plus capecitabine and epirubicin plus oxaliplatin plus capecitabine versus epirubicin plus cisplatin plus fluorouracil and epirubicin plus oxaliplatin plus fluorouracil. The ML17032 trial compared cisplatin plus capecitabine versus cisplatin plus fluorouracil. The trials demonstrated that capecitabine was as effective as fluorouracil for treating advanced gastric cancer with a similar tolerability profile. A current literature search for this review identified a phase 3, randomised controlled trial with 438 participants assessing the efficacy and safety of capecitabine plus oxaliplatin and fluorouracil plus oxaliplatin for treating advanced gastric cancer. This study is still at the recruitment phase and is expected to be completed in 2018.

Several phase 2 trials with small patient numbers were also identified from the literature which also shows that capecitabine and fluorouracil were similar in their efficacy and safety profiles in line with the REAL-2 and ML17032 trials. A meta-

analysis of 18 randomised controlled trials showed that capecitabine was associated with prolonged overall survival and enhanced response compared with fluorouracil. Another meta-analysis of individual data from 6171 patients confirmed the non-inferiority of capecitabine compared with fluorouracil for treating colorectal and gastric cancers. A cost-consequence analysis was also identified where the use of capecitabine was associated with decreased consumption of hospital resources compared with fluorouracil, although the acquisition cost of capecitabine was higher. The total incremental cost of the capecitabine triplet regimen compared with the fluorouracil triplet regimen was $508.

The literature search for this review proposal did not identify any other studies directly relevant to the decision problem for TA 191.

In conclusion, no new evidence has been identified that is likely to lead to a change in the recommendations of the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3. Hospital Pharmacy Audit Index cost and volume data for capecitabine show that uptake of capecitabine decreased slightly since TA 191 was published in July 2010; however, it is not possible to draw any firm conclusions about the use in gastric cancer from these data because the audit encompassed capecitabine's multiple indications.

9. Equality issues

The Committee acknowledged that some people with inoperable advanced gastric cancer may not be able to swallow oral capecitabine tablets because of difficulty with swallowing as a result of the cancer, or because of nausea. However the Committee noted that although capecitabine is preferred in most circumstances, fluorouracil remains an alternative where capecitabine is contraindicated or otherwise unsuitable. Therefore, it concluded that there were no specific issues relating to equality that needed to be taken into account.

GE paper sign off: Janet Robertson, 4 April 2013

Contributors to this paper:

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Appendix 1 – 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.	A review of the appraisal will be planned into 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
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated 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.	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

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. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Trastuzumab for the treatment of HER2-positive metastatic gastric cancer TA208. Published: November 2010. Review date: August 2013.

In progress

None

Referred - QSs and CGs

None

Suspended/terminated

None

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Capecitabine has a UK marketing authorisation for the first-line treatment of advanced gastric cancer in combination with a platinum-based regimen The cost of 60 150-mg tablets of capecitabine is £40.02 and the cost of 120 500-mg tablets is £265.55 (excluding VAT; Monthly Index of Medical Specialities [MIMS], March 2010).	No change (SPC, Nov 2012) The patent for capecitabine is due to expire in November 2013 and has not yet expired. Source: Letter from Roche (21 Jan 2013) Capecitabine 150 mg, net price 60-tab pack = £40.02; 500 mg, 120-tab pack = £265.55 (BNF, February 2013)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Lapatinib (GSK)	Phase III trials [redacted]
S-1 (tegafur + gimeracil + oteracil [teysuno] (Taiho)	UK launch Q2 2012 Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin (SPC, March 2011)
Onartuzumab (Roche)	Phase III trials started Nov 2012 and due to complete 2016 For metastatic her2-negative, met-positive gastroesophageal cancer
Pertuzumab (Roche)	Phase II clinical trials [redacted]For first-line treatment of metastatic HER2-positive adenocarcinoma of the stomach or gastroesophageal junction
Trastuzumab emtansine (Roche)	Phase III clinical trials [redacted]For HER2-positive advanced gastric cancer
Rilotumumab (Amgen)	Phase III clinical trial started Oct 2012. [redacted]For first-line therapy of advanced met-positive gastric or gastroesophageal junction adenocarcinoma
Telatinib (ACT Biotech)	Phase II clinical trials [redacted]For first-line gastric cancer

Registered and unpublished trials

Trial name and registration number	Details
A Randomized, Phase III, Multicenter Clinical Trial Comparing Capecitabine Plus Oxaliplatin (XELOX) and Capecitabine (X) as First-line Chemotherapy in Elderly Patients With Advanced Gastric Cancer NCT01470742	Enrolment: 200 Start date: September 2010 Status: Recruiting Location: South Korea Participants: Age ≥ 70
A Phase III Trial to Evaluate the Efficacy and Safety of the Combination Therapy of Capecitabine and Oxaliplatin (XELOX) in Comparison to the Combination Therapy of Fluorouracil/Folinic Acid and Oxaliplatin (FOLFOX) in Patients With AGC NCT01748851	Enrolment: 438 Start date: December 2012 Completion date: 2018 Status: Recruiting Location: South Korea
321GO: Three, two or one-drug chemotherapy for advanced gastroesophageal cancer: a feasibility study in frail and/or elderly patients ISRCTN33934807	Enrolment: 55 Completion date: 2011 Status: Completed Country: UK Brief overview of results

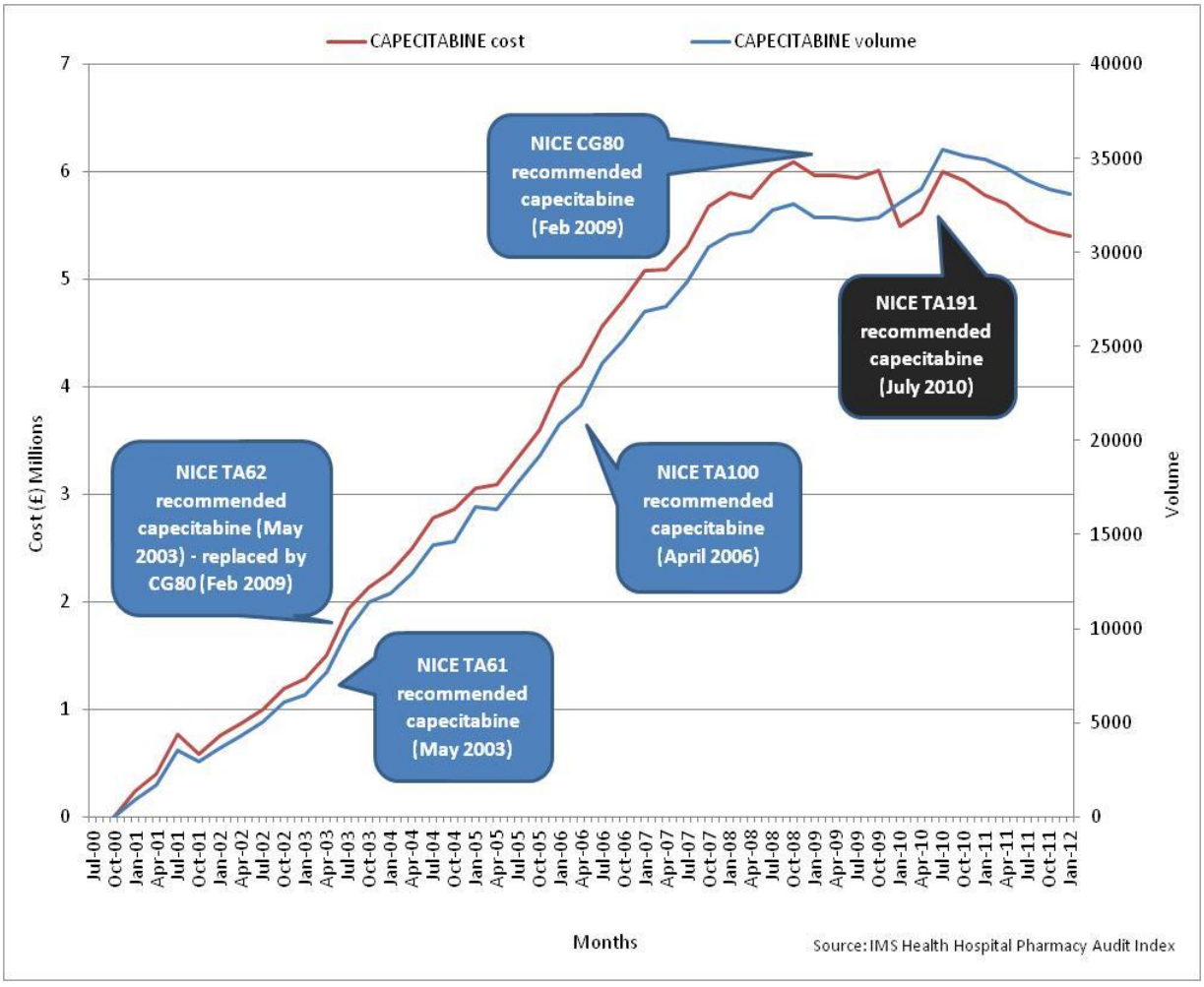
Appendix 3 – Implementation submission

1 Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of capecitabine prescribed and dispensed in hospitals in England between July 2000 and January 2012. These data should be treated with caution as there is more than one indication for capecitabine, therefore not only for gastric cancer.

Figure 1 Cost and volume of capecitabine prescribed and dispensed in hospitals in England



2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

2.1 Health and Social Care Information Centre (2012) Use of NICE-appraised medicines in the NHS in England - 2010 and 2011, Experimental Statistics

This is the 3rd report published by the HSCIC on behalf of the DH to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 52 medicines in 25 groups, relating to 35 technology appraisals were considered. Out of the 12 groups where a comparison could be made, observed use by the NHS in England was higher than the predicted use for 6 and lower for 6. For one drug group use was lower on one measure, and higher on another.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.

4 Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.