The Scottish Medicines Consortium 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

capecitabine (Xeloda®) is accepted for use within NHS Scotland for first line treatment of patients with advanced gastric cancer in combination with a platinum-based chemotherapy regimen.

Capecitabine was non-inferior to continuously infused intravenous 5-FU in terms of progression-free survival when each was used in combination with a platinum-based drug in patients with advanced gastric cancer. It also demonstrated non-inferiority in overall survival compared with continuously infused intravenous 5-FU in patients with advanced gastric cancer when each was used in a triple regimen containing a platinum-based drug and an anthracycline drug.

Capecitabine is more expensive than 5-FU, however, the convenience of oral administration may allow changes to service delivery that have individual patient or organisational benefits.

Overleaf is the detailed advice on this product.
**Indication**  
First line treatment of patients with advanced gastric cancer in combination with a platinum based chemotherapy regimen.

**Dosing information**  
In combination with a platinum-based compound, capecitabine should be administered twice daily at a dose of 1000 mg/m² for 14 days followed by a 7-day rest period. If epirubicin is added to this regimen, the recommended dose of capecitabine is 625 mg/m² twice daily continuously. Epirubicin at a dose of 50 mg/m² should be given on day 1 every 3 weeks. The platinum-based compound [cisplatin at a dose of 60 mg/m² (triple regimen) – 80 mg/m² (double regimen) or oxaliplatin at a dose of 130 mg/m²] should be given on day 1 every 3 weeks.

**Product availability date**  
March 2007

**Summary of evidence on comparative efficacy**  
Capecitabine is an orally administered non-cytotoxic fluoropyrimidine carbamate which acts as a pro-drug undergoing a three-step enzymatic conversion to the cytotoxic fluorouracil (5-FU). The initial metabolism takes place in the liver but the final conversion to 5-FU occurs at the tumour site. 5-FU acts by inhibiting thymidylate synthase, which is the rate-limiting enzyme in pyrimidine nucleotide synthesis, thus inhibiting DNA synthesis. This is a licence extension for capecitabine and is supported by data from two studies.

A phase III, open-label, multicentre, non-inferiority study used a 2 by 2 randomisation to compare oral capecitabine with continuously infused intravenous (IV) 5-FU, and oxaliplatin with cisplatin. Patients were included if they had inoperable locally advanced or metastatic adenocarcinoma, squamous cell carcinoma or undifferentiated carcinoma of the oesophagus, oesophagogastric junction or stomach; Eastern Cooperative Oncology Group performance status 0-2; no prior chemotherapy or radiotherapy unless the latter was adjuvant treatment with relapse outside the radiotherapy field and life expectancy ≥ 3 months.

1002 patients were randomised to one of the following 4 regimens and stratified for extent of disease (locally advanced or metastatic), performance status and study centre.

- ECF (epirubicin 50 mg/m² IV on day 1, cisplatin 60 mg/m² IV day on 1, 5-FU 200 mg/m² IV on days 1-21 as a continuous infusion via central line).
- ECX epirubicin 50 mg/m² IV on day 1, cisplatin 60 mg/m² IV on day 1, capecitabine 625 mg/m² orally twice daily on days 1-21.
- EOF epirubicin 50 mg/m² IV on day 1, oxaliplatin 130 mg/m² IV on day 1, 5-FU 200 mg/m² IV on days 1-21 as a continuous infusion via central line.
- EOX epirubicin 50 mg/m² IV on day 1, oxaliplatin 130 mg/m² IV on day 1, capecitabine 625 mg/m² orally twice daily on days 1-21.

All treatments were repeated every 3 weeks for 8 cycles in the absence of progressive disease or unacceptable toxicity. Tumour assessments were performed by CT scan at baseline, 12 weeks and 24 weeks.
The primary efficacy analysis in the per protocol population (n=964) demonstrated non-inferiority in overall survival for capecitabine- vs 5-FU- based regimens (hazard ratio (HR) 0.86, 95% CI: 0.75 to 0.99) (table 1). This was supported by the results from the intention-to-treat population (ITT). The median overall survival was 10.9 months in capecitabine-based regimens and 9.6 months in 5-FU based regimens.

Table 1: Overall survival results

<table>
<thead>
<tr>
<th>2x2 comparisons Per Protocol</th>
<th>1 year OS (95% CI)</th>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU: ECF + EOF</td>
<td>39.4% (35.0-43.7)</td>
<td>9.6</td>
<td>1</td>
</tr>
<tr>
<td>Capecitabine: ECX + EOX</td>
<td>44.6% (40.1-49.0)</td>
<td>10.9</td>
<td>0.86 (0.75-0.99)*</td>
</tr>
<tr>
<td>Regimens ITT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECF n=263</td>
<td>37.7% (31.8-43.6)</td>
<td>9.9</td>
<td>1</td>
</tr>
<tr>
<td>EOF n=245</td>
<td>40.4% (34.2-46.5)</td>
<td>9.3</td>
<td>0.95 (0.79-1.15)</td>
</tr>
<tr>
<td>ECX n=250</td>
<td>40.8% (34.7-46.9)</td>
<td>9.9</td>
<td>0.92 (0.76-1.11)</td>
</tr>
<tr>
<td>EOX n=244</td>
<td>46.8% (40.4-52.9)</td>
<td>11.2</td>
<td>0.80 (0.65-0.97)</td>
</tr>
</tbody>
</table>

* The upper limit of the 95% CI excludes 1.23 therefore non-inferiority was concluded ‡ p=0.025 comparison with ECF. CI, confidence interval; HR, hazard ratio; OS, overall survival

There were no significant differences between treatments in the secondary outcomes of progression free survival (PFS), tumour response or quality of life measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30.

In a second phase III, open label, multicentre study, 316 patients were randomised equally to the following treatment arms:

- CX (capecitabine 1000mg/m² twice daily days 1-14, cisplatin 80mg/m² IV day 1
- CF (5-FU 800mg/m² daily by continuous infusion on days 1-5, cisplatin 80mg/m² IV on day 1.

Inclusion criteria were: locally advanced and/or metastatic gastric adenocarcinoma; at least one measurable lesion according to Response Evaluation Criteria in Solid Tumours. (RECIST) that had not been irradiated; ambulatory; Karnofsky performance status ≥ 70%; life expectancy ≥ 3 months. The primary objective was to demonstrate the non-inferiority of the PFS with capecitabine/cisplatin compared with 5-FU (5-day infusion)/cisplatin. Treatment was repeated every 3 weeks until disease progression or unacceptable toxicity. Tumour assessments, using RECIST criteria, were performed at the end of every second cycle during treatment and at 3-month intervals after the end of treatment.

Capecitabine in combination with cisplatin was non-inferior to 5-FU in combination with cisplatin in terms of PFS in the per protocol analysis (HR 0.81; 95% CI 0.6-1.04). This was supported by the results from the ITT population (HR 0.80; 95% CI 0.63-1.03). The median PFS was 5.6 months for the capecitabine regimen vs 5.0 months for the 5-FU based regimen. For the secondary outcome of survival the HR for duration of survival (overall survival) was (HR 0.85; 95% CI 0.64 – 1.13) with a median duration of survival of 10.5 months (capecitabine + cisplatin) vs 9.3 months (5-FU + cisplatin).
Summary of evidence on comparative safety

No new safety concerns have arisen with the use of capecitabine in advanced gastric cancer. There was little difference between infused 5-FU and oral capecitabine on the overall number of adverse events experienced by patients or on the frequency of severe and life-threatening events.

The most notable difference was a significant increase in the frequency of hand-foot syndrome (palmar-plantar erythrodyssaeesthesia); 10.3% vs 4.3% for the ECX and EFC groups respectively in the 4-arm study. This syndrome is characteristic of prolonged fluoropyrimidine treatment and may necessitate dose reduction or interruption.

Toxicity did not limit the ability to administer treatment in either the 2-arm study where more treatment weeks were completed by CX than CF recipients or the 4-arm study where ECF and ECX patient groups both received a median of 6 treatment cycles and similar percentages of the planned 5-FU and capecitabine were delivered.

Summary of clinical effectiveness issues

Advanced gastric cancer is incurable and the aim of palliative chemotherapy is to increase survival, prevent symptomatic deterioration and improve quality of life. There is evidence that only those patients with good performance status benefit from invasive palliative intervention.

The trials cited above have demonstrated that replacing infused 5-FU with capecitabine in current treatment regimens for advanced gastric cancer does not compromise treatment outcomes or patient safety, although there was no evidence of quality of life benefit.

The inclusion of patients with cancer of the oesophagus and oesophagogastric junction in the 4-arm study would not be expected to significantly affect the results. In Scotland the treatment approach to these cancers is the same.

The results of the 4-arm study are particularly relevant to treatment in Scotland as it included patients from five Scottish hospitals and used the current standard treatment (ECF) in the control arm.

The use of capecitabine in place of 5-FU is likely to have a significant beneficial impact on patients and the health service. Benefits include ease of administration, avoidance of complications and safety issues associated with continuous intravenous infusion, potential reduction in number of hospital visits and reduced pressure on intravenous chemotherapy services.

Summary of comparative health economic evidence

The manufacturer submitted a cost minimisation analysis comparing oral capecitabine with IV 5-FU. A cost minimisation analysis was justified based on equivalent efficacy being demonstrated in the key clinical trial. The results of the base case analysis showed that changing from treatment with IV 5-FU to oral capecitabine resulted in an additional £633 in drug acquisition costs and a saving of £1,773 in drug administration costs. This resulted in an overall saving of £1,139 per patient per course.
SMC guidance indicates that a cost minimisation analysis is appropriate when there is evidence of equivalent efficacy between the new treatment and current clinical practice. The clinical evidence supported the assumption that oral capecitabine had equivalent efficacy to IV 5-FU, therefore a cost minimisation analysis was appropriate.

The range of health care resources included in the submission for patients on ECF was extensive and appeared to include all relevant resources. In general, appropriate sources were used to estimate resource use and unit costs. The results showed that under a range of scenarios, oral capecitabine appears to represent a cost effective alternative to IV 5-FU.

**Summary of patient and public involvement**

A Patient Interest group Submission was not made.

**Additional information: guidelines and protocols**

In June 2006 the Scottish Intercollegiate Guidelines Network (SIGN) published Guideline 87 Management of oesophageal and gastric cancer which states that in patients with locally advanced or metastatic cancer of the oesophagus or stomach with good performance status combination chemotherapy including cisplatin and infusional 5-FU (such as ECF or MCF) should be considered. This guideline predates the licence of capecitabine for advanced gastric cancer.

**Additional information: previous SMC advice**

In October 2006, in the absence of a submission from the holder of the marketing authorisation, the SMC advised that: docetaxel (Taxotere) injection concentrate in combination with cisplatin and 5-fluorouracil is not recommended for use within NHS Scotland for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

**Additional information: comparators**

The only relevant comparator is 5-FU.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per cycle* (£)</th>
<th>Cost per course**</th>
</tr>
</thead>
<tbody>
<tr>
<td>capecitabine</td>
<td>625mg/m² orally twice daily (days 1-21)</td>
<td>238</td>
<td>1904</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>200mg/m² continuous intravenous infusion daily (days 1-21)</td>
<td>106</td>
<td>848</td>
</tr>
<tr>
<td>capecitabine</td>
<td>1000mg/m² orally twice daily (days 1-14)</td>
<td>248</td>
<td>1984</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>800mg/m² continuous intravenous infusion daily (days 1-5)</td>
<td>93</td>
<td>744</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs for capecitabine from eVadis on 31.5.07. Costs for 5-fluorouracil from BNF (March 2007) and based on weekly replenishment of infusion pump. Doses based on body surface area 1.8m². *cycle duration = 3 weeks; ** cost based on course of 8 cycles as per 4-arm study. The epirubicin and platinum-based compound doses are not dependent on whether 5-fluorouracil or capecitabine is used.

Additional information: budget impact

The manufacturer estimated that the direct drug cost of oral capecitabine would be £32k in year 1, rising to £169k in year 5, based on patients receiving 1 course of chemotherapy and each course being completed in the year of commencement. The estimated savings due to reduced administration costs were £90k in year 1 and £472k in year 5. This resulted in a net saving of £58k in year 1 and £303k in year 5. These estimates were based on 101 patients receiving oral capecitabine in year 1 and 367 patients in year 5. The manufacturer assumed a market share of 22% in year 1 and 80% in year 5.
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.

This assessment is based on data submitted by the applicant company up to and including 12 July 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.