capecitabine 150mg and 500mg tablets (Xeloda®) No. (507/08)
Roche Products Limited

05 September 2008

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 the treatment of metastatic colorectal cancer.

The convenience of oral administration may allow changes to service delivery that have individual patient or organisational benefits, though these may be lessened when it is used in regimens whose other components require intravenous administration.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of metastatic colorectal cancer.

Dosing information

Monotherapy: capecitabine 1250 mg/m^2 administered twice daily for 14 days followed by a 7-day rest period.

Combination therapy: capecitabine 800 to 1000 mg/m^2 administered twice daily for 14 days followed by a 7-day rest period.

Product availability date

February 2008

Summary of evidence on comparative efficacy

The licensed indication for capecitabine, an oral fluoropyrimidine agent, has recently changed so that it may now be used as monotherapy or combination therapy in first- and second-line treatment of metastatic colorectal cancer (mCRC). This has replaced the previous indication, first-line monotherapy of mCRC. Data to support the first-line monotherapy use have not been included in the detailed advice document as this indication predated SMC and is therefore not within SMC's remit.

Two pivotal phase III open label studies in the first- and second-line settings supported the change in indication. The studies recruited adult patients with a histologically confirmed mCRC not previously treated in the first-line study, and following failure of first-line therapy with an irinotecan based regimen in the second-line study. Patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 in the first-line study and 0 to 2 in the second-line study. Patients were randomised to oral capecitabine plus oxaliplatin IV (XELOX) administered every 3 weeks or fluorouracil IV plus folinic acid IV plus oxaliplatin IV (FOLFOX-4) administered every 2 weeks (see cost table for doses) for at least 48 weeks in the first-line study and up to 24 weeks in the second-line study. The intention to treat (ITT) population was used for the superiority analyses and in the first-line study the eligible patient population (EPP), which excluded patients from the ITT population who had violated major protocol inclusion and exclusion criteria or who did not receive at least one dose of study medication, was used for the non-inferiority analysis. In the second-line study the per protocol population (PPP) defined as the ITT minus major protocol violators and patients not receiving at least 2 cycles of XELOX and 3 cycles of FOLFOX-4 (due to reasons other than progressive disease) was used for the non-inferiority analysis. Secondary endpoints for both studies included overall survival (OS).

In the first-line study following randomisation of 634 patients, the study was amended to include a 2x2 partially blinded design. Bevacizumab 7.5mg/kg or placebo IV was added to each cycle of XELOX and an equivalent dose to FOLFOX-4. The first of the two co-primary endpoints was the non-inferiority of the pooled XELOX versus FOLFOX-4 containing arms for progression free survival (PFS); non-inferiority was concluded if the upper limit of the 97.5% confidence interval (CI) for the hazard ratio (HR) was ≤ 1.23. The second co-primary endpoint involved bevacizumab and is not reported here. The median PFSs for the XELOX and FOLFOX-4 containing arms were 7.9 and 8.5 months respectively and non-inferiority of XELOX versus FOLFOX-4 was concluded. Results for PFS and OS are reported in the table below.

In the second-line study the primary endpoint was non-inferiority of XELOX compared with FOLFOX-4 for PFS and was concluded if the upper limit of the two-sided 95% CI for the HR was ≤ 1.3. The median PFSs were 5.1 and 5.5 months for XELOX and FOLFOX-4 arms respectively and non-inferiority was concluded. Results for PFS and OS are reported in the table below.

Table: Progression free survival (PFS) and overall survival (OS) for the first- and second-line studies comparing XELOX and FOLFOX-4 (pooled arms in first-line study) in the treatment of metastatic colorectal cancer

First line study	**Pooled XELOX arms**	**Pooled FOLFOX-4 arms**	**HR (confidence interval [CI])**
n (EPP)	967	937	
Median PFS (months)	7.9	8.5	1.05 (97.5% CI 0.94 to 1.18)
n (ITT)	1017	1017	
Median OS (months)	19.8	19.6	0.99 (97.5% CI 0.88 to 1.12)
Second line study	**XELOX**	**FOLFOX-4**	**HR (confidence interval [CI])**
n (PPP)	251	252	
Median PFS (months)	5.1	5.5	1.03 (95% CI 0.84 to 1.24)
n (ITT)	313	314	
Median OS (months) ITT	11.9	12.6	1.03 (95% CI 0.87 to 1.23)

XELOX= capecitabine + oxaliplatin, FOLFOX-4= fluorouracil + folinic acid + oxaliplatin. EPP=eligible patient population, ITT=intention to treat population, PPP=per protocol population.

In addition, phase III trials have investigated first-line treatment of capecitabine in combination with irinotecan, and phase II studies have investigated second-line treatment with capecitabine monotherapy and in combination with irinotecan.

Summary of evidence on comparative safety

No new safety concerns were observed in the pivotal phase III studies.

In the first-line study the safety assessment of XELOX versus FOLFOX-4 was taken from the pooled XELOX/XELOX + placebo and FOLFOX-4/FOLFOX-4 + placebo arms. Grade 3/4 neutropenia was reported in 45 (6.9%) and 279 (43%) of patients in the XELOX and FOLFOX-4 containing arms and febrile neutropenia in 0.9% and 4.8% of patients respectively. However grade 3/4 diarrhoea (n=132 [20%] vs. n=73 [11%]) and grade 3 hand-foot syndrome (n=40 [6.1%] vs. n=8 [1.2%]) were more common with XELOX compared with FOLFOX-4 treated patients. The incidence of grade 3/4 neurosensory toxicity was similar in both groups (approximately 17%). Thus the European Medicines Agency (EMEA) concluded that the safety data for XELOX do not suggest a safety profile relevantly different from FOLFOX-4 other than the known differences between capecitabine and fluorouracil; the haematological adverse events of FOLFOX-4 are replaced by diarrhoea and hand-foot syndrome associated with XELOX.

Summary of clinical effectiveness issues

In the pivotal studies, patients were relatively young (median age 60 to 62 years) and, in the first-line study, had an ECOG PS of ≤ 1. However Cancer Registry data from patients in Scotland in 2004 indicate that 73% and 59% of patients diagnosed with colorectal cancer were aged at least 65 years and at least 70 years respectively. It is possible that the benefits observed in these studies may be different to those observed in the Scottish population eligible for treatment.

In the first-line study, results for PFS determined by the independent review committee (IRC) were not supportive of the non-inferiority analysis. In the comparison of the pooled XELOX and FOLFOX-4 containing arms the HR was 1.22 (97.5% CI 1.05 to 1.42). However the EMEA considered the IRC assessments, which used different criteria, to be more open to bias and concluded that non-inferiority had been shown.

There are limited data to support the second-line use of capecitabine monotherapy, and capecitabine in combination with irinotecan in the treatment of mCRC. The EMEA concluded that overall the risk-benefit relationship of capecitabine in mCRC is acceptable and comparable to 5-FU [fluorouracil] and therefore a general indication for capecitabine "in the treatment of metastatic colorectal cancer" was supported.

The EMEA commented that in combination therapy the advantage of oral administration of capecitabine is less relevant than in monotherapy as the combination agent is administered intravenously. Patients receiving XELOX will, however, require a single visit to hospital per cycle (for administration of oxaliplatin), compared with FOLFOX-4 where most patients will require central venous access and two visits per cycle. Therefore XELOX may offer advantages over regimens that contain drugs administered solely by the intravenous route by allowing changes to service delivery.

The marketing authorisations for oxaliplatin and irinotecan cover only their use in combination with 5-fluorouracil and folinic acid for the treatment of metastatic colorectal cancer, and for first-line use only for irinotecan. Neither drug is licensed for use in combination with capecitabine.

The EMEA noted that it appears that 5-FU can in general be replaced by capecitabine while not affecting the efficacy profile but changing the safety profile in line with known differences between these agents.

Summary of comparative health economic evidence

The manufacturer presented cost-minimisation analyses of capecitabine monotherapy and capecitabine in combination with oxaliplatin (XELOX) or irinotecan (XELIRI) for patients with metastatic colorectal cancer. Five economic analyses were carried out to cover the broadening of the licence:

1. XELOX vs. FOLFOX-4 – first-line
2. XELOX vs. FOLFOX-4 – second-line
3. XELIRI vs. FOLFIRI – first-line
4. XELIRI vs. FOLFIRI – second-line
5. Capecitabine monotherapy vs. modified de Gramont regimen – second-line

(where FOLFIRI is fluorouracil, folinic acid and irinotecan).

The main clinical data sources were the pivotal phase III trials of XELOX vs. FOLFOX-4 in first-line and second-line use which showed XELOX was non-inferior to FOLFOX-4. Indirect comparisons were carried out for the other three comparisons. The manufacturer estimated that changing to capecitabine would result in savings in each scenario of between £3k and £10k per patient.

Whilst XELOX has now largely replaced FOLFOX-4 for first-line treatment of mCRC in Scotland, the comparators used appear to be appropriate and experts have confirmed that they are relevant to Scottish practice. The resource use estimates have been largely verified

by clinical experts and the responses indicated that while there may be some variation across Scotland, overall the assumptions used by the manufacturer were reasonable.

The main weakness was the indirect comparison with FOLFIRI and the modified de Gramont regimen but any biases are unlikely to be sufficient to alter the conclusions.

Overall, treatment with oral capecitabine in place of 5-FU appears to result in resource use and administration savings largely due to the regimens being administered on a day-case basis rather than as an inpatient stay.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 67, Management of Colorectal Cancer; a national clinical guideline in March 2003. A review report in 2007 indicated that the guideline may require revision in the light of new evidence.

The National Institute for Health and Clinical Excellence (NICE) technology appraisal 61, Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer, was published in May 2003. Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.

NICE issued technology appraisal 93, Irinotecan, oxaliplatin and ralitrexed for the treatment of advanced colorectal cancer, in August 2005. Irinotecan is recommended as a treatment option for people with advanced colorectal cancer in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy and oxaliplatin is recommended in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.

NICE have a guideline in development; Diagnosis and management of colorectal and anal cancer, listed on their website. The date of publication is to be confirmed. The remit, agreed on 18 September 2007, is the diagnosis and management of patients with all stages of primary colorectal and anal cancer.

Additional information: previous SMC advice

Following a full submission SMC published advice in June 2008: bevacizumab (Avastin) is not recommended for use within NHS Scotland in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum. In a randomised trial standard chemotherapy plus bevacizumab showed a small benefit over standard chemotherapy alone in terms of progression-free survival. However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Following an Independent Review Panel SMC published advice in October 2005: cetuximab (Erbitux®) is not recommended for use within NHS Scotland in combination with irinotecan

for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Additional information: comparators

NICE has recommended a number of different regimens for mCRC or advanced CRC including capecitabine, tegafur/uracil plus folinic acid, oxaliplatin/fluorouracil/folinic acid and irinotecan/fluorouracil/folinic acid. SMC experts suggested that XELOX, FOLFOX-4, and capecitabine alone are being used in Scotland for the treatment of mCRC.

Cost of relevant comparators

Name of regimen	Dose regimen (where D1 = Day 1)	Cycle length	Cost per cycle (£)	Cost per 26 weeks (£)
Capecitabine monotherapy	**capecitabine 1250 mg/m^2 orally twice daily D1 to 14**	**3 weeks**	**310**	**2,480**
XELOX	**oxaliplatin 130 mg/m^2 IV D1 capecitabine 1000mg/m^2 orally twice daily D1 to 14**	**3 weeks**	**1,073**	**8,584**
XELIRI	**irinotecan 250 mg/m^2 on D1 capecitabine 1000mg/m^2 orally twice daily D1 to 14**	**3 weeks**	**874**	**6,992**
FOLFOX-4	fluorouracil 400 mg/m^2 IV bolus, 600 mg/m^2 IV infusion D1, 2 folinic acid 200 mg/m^2 IV infusion D1, 2 oxaliplatin 85 mg/m^2 IV infusion D1	2 weeks	922	12,116
IFL, Saltz	fluorouracil 500 mg/m^2 IV D1, 8, 15, 22 folinic acid 20 mg/m^2 IV D1, 8, 15, 22 irinotecan 125 mg/m^2 D1, 8, 15, 22	6 weeks	1,381	5,524
De Gramont	fluorouracil 400 mg/m^2 IV bolus, 600 mg/m^2 IV infusion D1, 2 folinic acid 200 mg/m^2 IV D1, 2	2 weeks	239	3,109

Doses are for general comparison and do not imply therapeutic equivalence.
Costs obtained from BNF no 55 (March 2008) and eVadis (30/6/08).
Costs are based on a body weight of 80kg and a body surface area of 1.8m^2. Costs per 26 weeks are the costs of compete cycles, which would be administered during a 26-week period.
Oxaliplatin and irinotecan are not licensed for combination with capecitabine. Not all regimens used in the treatment of mCRC are included in the table.

Additional information: budget impact

The following budget impact estimates were made by the manufacturer:

First-line use:

- XELOX replacing FOLFOX – net drug budget estimated savings of £91k in year 1 rising to £208k in year 5. Including savings from reduced administration costs results in net budget savings of £1.5m rising to £3.5m. These estimates were based on 158 patients in year 1 rising to 360 in year 5.
- XELIRI replacing FOLFIRI – net drug budget estimated savings of £69k in year 1 rising to £157k in year 5. Including savings from reduced administration costs results in net budget savings of £608k rising to £1.4m. These estimates were based on 60 patients rising to 137 in year 5.

Second-line combination use:

- XELOX replacing FOLFOX – net drug budget savings of £8k in year 1 rising to £18k in year 5. Including savings from reduced administration costs results in net budget savings of £99k rising to £226k. These estimates were based on 15 patients in year 1 rising to 35 in year 5
- XELIRI replacing FOLFIRI – net drug budget savings of £44k in year 1 rising to £100k in year 5. Including savings from reduced administration costs results in net budget savings of £90k rising to £207k. These estimates were based on 27 patients rising to 61 in year 5.

Second-line monotherapy:

- Capecitabine replacing modified de Gramont regimen – net drug budget savings of £2k in year 1 rising to £4k in year 5. Including savings from reduced administration costs results in net budget savings of £31k rising to £70k. These estimates were based on 6 patients in year one rising to 14 patients in year five.

A market share of 35% in year 1 rising to 80% in year 5 was assumed for all estimates. These projections of market share are likely to be underestimates as feedback from clinical experts indicated that capecitabine is already widely used. As a result the savings from switching from IV 5-FU to oral capecitabine are already likely to have been realised in most centres.

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 15 August 2008.

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.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Cassidy J *et al*. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008; 26 (12): 2006-2012.

Rothenberg ML et al. Phase III trial of capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2nd-line treatment for patients with metastatic colorectal cancer (MCRC). Am Soc Clin Oncol Annual Meeting 2007; Abstract 4031.

The European Medicines Agency (EMEA) European Public Assessment Report. Xeloda EMEA/H/C/000316/II/0028. Accessed on 2/7/08 http://www.emea.europa.eu/humandocs/Humans/EPAR/xeloda/xelodaM2.htm