Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Angela Timoney FRPharmS

capecitabine, 150mg, 500mg, tablets (Xeloda®) SMC No. (716/11)
Roche Products Limited

08 July 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

capecitabine (Xeloda®) is accepted for use within NHS Scotland.

Indication under review: The adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer in combination with oxaliplatin.

At 55 months, disease free survival was significantly increased for capecitabine plus oxaliplatin-treated patients compared with a recognised regimen containing a fluoropyramidine in the adjuvant treatment of patients with completely resected stage III (Dukes' C) colon cancer.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. (Extension to marketing authorisation to include the use of capecitabine in combination with oxaliplatin).

Dosing Information

In combination with oxaliplatin, the recommended starting dose of Xeloda should be 800 to 1,000mg/m^2 administered twice daily for 14 days followed by a seven-day rest period. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of six months.

Product availability date

March 2011

Summary of evidence on comparative efficacy

Capecitabine is an oral fluoropyrimidine agent, a pro-drug that undergoes enzymatic conversion to fluorouracil (5-FU). Fluorouracil acts by inhibiting thymidylate synthase, interfering with the production of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein, provoking the death of a cell, particularly rapidly proliferating cells (e.g. cancers).

Capecitabine has been previously accepted for use by the Scottish Medicines Consortium (SMC) as monotherapy for adjuvant treatment of stage III colon cancer. The indication under review is an extension to the licensed indication for the adjuvant treatment of stage III colon cancer, when used in combination with oxaliplatin.

Evidence comes from an open-label, randomised, active-controlled, phase III study. Recruited patients were ≥18 years of age with histologically confirmed stage III colon cancer (fully recovered from surgery that took place no more than eight weeks previously), with an Eastern Cooperative Oncology Group (ECOG) performance status of zero or one. Patients were equally assigned to either CapOx (oxaliplatin 130mg/m^2 intravenous infusion over two hours on day one plus oral capecitabine 1,000mg/m^2 twice daily on days 1 to 14 of a three-week cycle for eight cycles); or 5-FU/FA (bolus fluorouracil plus folinic acid) given as either the Mayo Clinic or Roswell Park regimen. The choice of 5-FU/FA regimen was pre-specified for each treatment centre prior to commencement of the study. The Mayo Clinic regimen consisted of a rapid infusion of FA (20mg/m^2) followed by an intravenous bolus of 5-FU 425mg/m^2 on days one to five of a four-week cycle for six cycles. The Roswell Park regimen consisted of a two-hour infusion of FA (500mg/m^2) plus an intravenous bolus of 5-FU 500mg/m^2 on day one of weeks one to six of an eight-week cycle for four cycles.

The primary outcome assessed in the intention-to-treat population, was disease-free survival (DFS) defined as the time between randomisation and recurrence, or the occurrence of a new primary colon cancer, death from any cause, or the last date at which the patient was known to be disease-free. The study had a pre-defined clinical cut-off and after a median follow-up of 55 months the proportion of patients that had relapsed, developed a new colon cancer, or died was

31% (295/944) in the CapOx group and 38% (353/942) in the 5-FU/FA group, giving an estimated hazard ratio (HR) for DFS for patients treated with CapOx compared with 5-FU/FA of 0.80 (95% confidence interval [CI]: 0.69 to 0.93). The three-year DFS rate for CapOx was 71% (95% CI: 68 to 74%) and for 5-FU/FA 67% (95% CI: 63 to 70%).

Secondary endpoints in the study were overall survival and relapse-free survival. There was no statistically significant difference in overall survival, defined as the time from randomisation to death or the last date at which the patient was known to be alive, between CapOx and 5-FU/FA after 57 months of follow-up. At this point 21% (197/944) of patients in the CapOx group had died, compared to 24% (225/942) of patients randomised to 5-FU/FA; HR 0.87 (95% CI: 0.72 to 1.05). Relapse-free survival was defined as the time from randomisation to first relapse, new primary colon cancer, and death due to treatment-related toxicity or colon cancer if relapse had not been documented and favoured CapOx over 5-FU/FA; HR 0.78 (95% CI: 0.67 to 0.92).

Summary of evidence on comparative safety

The majority of patients in the study reported at least one treatment-related adverse event, significantly more in the CapOx group (98% [921/938]) compared to the 5-FU/FA group (94% [873/926]). Patients in the CapOx group experienced more neurosensory toxicity (78% versus 7%), vomiting (43% versus 25%), anorexia (24% versus 18%), and hand-foot syndrome (29% versus 10%). However they were less likely to report diarrhoea (60% versus 72%), stomatitis (21% versus 51%) or alopecia (4% versus 20%).

Treatment-related adverse events with severity grades three and four were also reported of which significantly more patients in the CapOx group experienced these events compared with the 5-FU/FA group (55% versus 47%). Patients treated with CapOx were more likely to experience neurosensory toxicity (11% versus <1%), vomiting (6% versus 3%), hand-foot syndrome (5% versus <1%) and thrombocytopenia (5% versus <1%). They were less likely to experience neutropenia (9% versus 16%), febrile neutropenia (<1% versus 4%), and stomatitis (<1% versus 9%). Oxaliplatin is primarily associated with neurosensory toxicity.

Patients over 65 years of age were more likely to withdraw from treatment due to adverse events and to suffer serious adverse events related to CapOx, specifically: diarrhoea, dehydration, and infection.

In total, there were 12 treatment-related deaths within four weeks of the last dose of study medication, six in each group.

Summary of clinical effectiveness issues

The pivotal study demonstrated that the capecitabine plus oxaliplatin regimen (CapOx) was significantly superior to the 5-FU/FA regimen for disease-free survival, resulting in a 20% relative risk reduction. There was no difference in the secondary outcome of overall survival between the two groups but the study was not powered and the data was insufficiently mature to detect a difference in this endpoint.

At the time of study design bolus 5-FU/FA was considered a first-line option as adjuvant chemotherapy for colon cancer. Studies since have shown that 5-FU/FA in combination with

oxaliplatin provides greater clinical benefit compared with 5-FU/FA and this strategy (either as FOLFOX or FLOX regimens) has been adopted as the recommended adjuvant treatment for stage III and 'high-risk' stage II colon cancer by the European Society for Medical Oncology in their guidelines published in 2010. Therefore the submitting company presented a Bayesian mixed treatment comparison to indirectly compare the efficacy of CapOx with the currently recommended regimens (FOLFOX, FLOX) as well as infusional 5-FU/FA, and capecitabine monotherapy. The results of this indirect comparison indicate that CapOx is similar to these regimens in efficacy in terms of disease-free survival at 3 years and overall survival at 5 years.

A naïve indirect comparison of the safety profiles of CapOx and FOLFOX as adjuvant therapies for colon cancer suggested some differences between the regimens. CapOx was associated with more hand-foot syndrome, skin adverse events and severe diarrhoea but conferred less stomatitis and myelotoxicity than FOLFOX.

The CapOx regimen requires one visit to the hospital/clinic every three weeks, however FOLFOX regimens require either one or two visits to the hospital/clinic every fortnight. Patients treated with infusional 5-FU will routinely have a central venous access device (CVAD) inserted, which has accompanying risks and responsibilities. For the CapOx regimen the reduction in hospital visits and cytotoxic parenteral therapies, and no requirement for CVAD may offer benefits for patients and for service delivery.

Summary of comparative health economic evidence

The submitting company provided a cost-minimisation analysis comparing CapOx to FOLFOX-4 and FOLFOX-6 for the treatment of patients with Stage III (Dukes C) cancer of the colon eligible for adjuvant oxaliplatin-containing combination chemotherapy. The time horizon was selected for the base-case based on the mean number of cycles of treatment used in the key clinical trials. This corresponded to 6.7 cycles of CapOx and 10.7 cycles for the FOLFOX regimens.

The clinical evidence demonstrating equivalent efficacy between CapOx and FOLFOX came from a mixed treatment comparison.

In terms of resource use, the analysis compared the drug acquisition, administration and pharmacy costs associated with each regimen.

The results showed the total direct cost was £6,763 per patient treated with CapOx and £13,253 and £16,541 per patient treated with FOLFOX-6 and FOLFOX-4 respectively. The company therefore claimed that CapOx was associated with cost savings of £6,490 and £9,778 respectively and would therefore be the preferred treatment on cost-minimisation grounds. The savings arose due to reduced costs associated with drug acquisition, central venous access devices (CVAD) for 5-FU, drug administration and pharmacy preparation time.

The key finding from the sensitivity analysis was that the estimated base case results were most sensitive to pharmacy costs and the cost of administration. CapOx was however cost-saving under all scenarios explored.

The key limitation of the analysis was that there was no head-to-head data directly comparing CapOx to FOLFOX.

Despite this limitation, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Society for Medical Oncology guidelines on primary colon cancer were published in April 2010. These guidelines recommend adjuvant treatment for stage III and 'high-risk' stage II patients. Following surgical intervention the adjuvant regimen recommended is oxaliplatin and 5-FU and FA (either the FOLFOX4 or FLOX schedules). Mono-therapy with 5-FU and FA, or capecitabine can be used if oxaliplatin is contra-indicated.

The guideline noted that capecitabine and oxaliplatin in combination have been evaluated in a range of different schedules and doses. The XELOXA international phase III study assessed the safety and efficacy of adjuvant capecitabine plus oxaliplatin (CapOx) versus bolus 5-FU/FA (Mayo Clinic or Roswell Park regimen). The toxicity profile was different: patients receiving CapOx experienced less all-grade diarrhoea, alopecia, and more neurosensitive toxicity, vomiting and hand–foot syndrome. Preliminary data of efficacy, presented at the moment only as an abstract, indicated a benefit in disease-free survival for CapOx.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 67 "Management of colorectal cancer" was published in 2003. The guideline recommends that patients with Dukes' C (stage III) tumours of the colon or rectum should be considered for adjuvant chemotherapy and the recommended adjuvant regimen is bolus fluorouracil and low-dose folinic acid (FUFA), administered over five days every four weeks. The duration of treatment should be six months. An update is in progress, and expected to be complete by winter 2011.

These guidelines pre-date the publication of results of capecitabine study and the extension to licensed indication currently under review by SMC.

Additional information: comparators

Other medicines used in the treatment of adjuvant colon cancer include: capecitabine (as monotherapy), 5-FU/FA, and oxaliplatin in combination with 5-FU/FA (e.g. FOLFOX).

Cost of relevant comparators

Regimen	Dose Regimen	Cost per cycle (£)	Cost per course (£)
CapOx (capecitabine tablets and oxaliplatin injection)	**Oxaliplatin 130mg/m^2 iv infusion on day 1. Capecitabine 1,000mg/m^2 orally every 12 hours from day 1 to 14. Cycle every 21 days for 6 months (8 cycles).**	**972**	**7,778**
FOLFOX-6 (fluorouracil, folinic acid, and oxaliplatin)	Oxaliplatin 100mg/m^2 iv infusion on day 1. Folinic acid 200mg/m^2 iv infusion on day 1. Fluorouracil 400mg/m^2 iv bolus on day 1. Fluorouracil 2,400mg/m^2 iv infusion from day 1. Cycle every 14 days for 6 months (12 cycles).	757	9,086
FOLFOX-4 (fluorouracil, folinic acid and oxaliplatin)	Oxaliplatin 85mg/m^2 iv infusion on day 1. Folinic acid 200mg/m^2 iv infusion on day 1 and 2. Fluorouracil 400mg/m^2 iv bolus on day 1 and 2. Fluorouracil 600mg/m^2 iv infusion on day 1 and 2. Cycle every 14 days for 6 months (12 cycles).	679	8,154
Capecitabine	1,250mg/m^2 orally twice daily for 14 days. Cycle every 21 days for 6 months (8 cycles).	279	2,230
5-Fluorouracil plus folinic acid	Folinic acid 20mg/m^2 iv injection and 5-FU 425mg/m^2 iv injection on days 1 to 5. Cycle every 28 days for 6 months (6 cycles).	110	660

Doses are for general comparison and do not imply therapeutic equivalence. Doses based on a body surface area of 1.8m^2. Costs from eVadis on 4 May 2011 and from BNF 61 (March 2011).
iv = intravenous

Additional information: budget impact

The company estimated the population eligible for treatment to be 118 patients. Based on an estimated uptake of 100% per year, the impact on the medicines budget was estimated at £635K per year. The net medicines budget impact was estimated at -£175K per year. Responses received from clinical experts have indicated that 118 eligible patients seem quite low and that some of these savings are likely to already have been realised in practice.

References

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

Schmoll HJ, Cartright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J Clin Oncol* 2007;25:102-9.

Haller D, Tabernero J, Maroun J, *et al*. First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study). *Eur J Cancer Supplements.* 2009;7(3):4.

Haller D, Tabernero J, Maroun J, *et al*. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011;29:1465-71.

This assessment is based on data submitted by the applicant company up to and including 26 May 2011.

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. 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.

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.