AWMSG Secretariat Assessment Report – Advice no. 0511
Capecitabine (Xeloda®) in combination with oxaliplatin for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer

This assessment report is based on evidence submitted by Roche Products Ltd on 01 November 2010

1.0 PRODUCT DETAILS

Licensed indication	Capecitabine (Xeloda®) for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer[1]. This submission only considers the recent licence extension for the use of capecitabine in combination with oxaliplatin for the adjuvant treatment of stage III (Dukes' stage C) colon cancer[2].
Dosing	Capecitabine tablets should be swallowed with water 30 minutes after a meal. In combination treatment, the recommended starting dose of capecitabine in the adjuvant treatment of stage III colon cancer is 800–1000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period, or 625 mg/m^2 twice daily when administered continuously[1]. Premedication with anti-emetics according to the oxaliplatin summary of product characteristics is recommended[3]. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of six months[1].
Marketing authorisation date	23 March 2010[1,2]
UK Launch date	23 March 2010[2]

2.0 DECISION CONTEXT

2.1 Background

Colon cancers are malignant growths arising from the large intestine and, together with rectal cancers, are the third most common cancer in the UK[4]. The incidence of colorectal cancer in the UK is approximately 46 per 100,000[5], and around 26% of these patients are classified as having stage III cancer (see Glossary for colon cancer staging criteria)[4]. Surgery to remove the primary tumour is the first line therapy in the majority of these patients[6], after which patients with stage III colon cancer exhibit a 50–60% chance of developing recurrent disease[4]. Systemic chemotherapy following surgery is recommended for patients with stage III colon cancer considered fit enough to tolerate it[6]. Recent guidelines from the European Society for Medical Oncology (ESMO) suggests that following surgery the standard treatment for patients is combination therapy with oxaliplatin, 5–fluorouracil (5-FU) and folinic acid (FA).[7]

Capecitabine is an oral prodrug of the fluoropyrimidine 5-FU, which is converted through a cascade of three enzymes: carboxylesterase, cytidine deaminase and finally thymidine phosphorylase[1]. Thymidine phosphorylase has been found to be

concentrated in several tumour tissues, including colorectal cancers, aiding tumour targeting and resulting in high intratumoural drug levels[1,2].

Capecitabine received market authorisation from the European Medicines Agency (EMA) for the adjuvant treatment of patients following surgery of stage III colon cancer in March 2005; this was extended to include combination therapy in March 2010. As requested by the Welsh Medicines Partnership (WMP) the company submission considers this licence extension for the use of capecitabine in combination with oxaliplatin for the adjuvant treatment of stage III colon cancer[2].

2.2 Comparators

The comparator requested by the WMP is infusional 5-FU in combination with FA and oxaliplatin chemotherapy (FOLFOX).

2.3 Guidance and related advice

- European Society for Medical Oncology: Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up (2010)[7]
- Association of Coloproctology of Great Britain and Ireland: Guidelines for the Management of Colorectal Cancer 3rd edition (2007)[8]
- National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Colon cancer (adjuvant) - capecitabine and oxaliplatin (2006)[4]
- National Institute for Health and Clinical Excellence (NICE): Cancer Services Guidance — Improving Outcomes in Colorectal Cancers (2004)[6]
- Scottish Intercollegiate Guidelines Network Guidelines (SIGN): Management of colorectal cancer (2003)[9]

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission is based on an indirect comparison of capecitabine and oxaliplatin combination therapy (XELOX) and FOLFOX-4[2]. This indirect analysis includes the NO16968 (XELOXA) trial and the MOSAIC trial. The NO16968 trial was designed to compare the clinical efficacy and safety profiles of XELOX and bolus regimens of 5-FU plus FA as adjuvant treatments for stage III colon cancer[2,10]. The MOSAIC trial evaluated the clinical efficacy and safety of the FOLFOX-4 regimen against infusional 5-FU plus FA in patients with resected colon cancer[11,12]. Additionally, the company submission includes a network meta-analysis which compares the XELOX combination treatment to other regimens currently used for the adjuvant treatment of stage III colon cancer[2].

3.1 Indirect comparison of the NO16968 (XELOXA) and MOSAIC studies

3.1.1 NO16968: Objectives, Design and Results

This open-label, multicentre phase III study was designed to demonstrate the superior clinical efficacy and safety profile of XELOX compared to 5-FU plus FA in chemotherapy-naive patients that had undergone surgery for stage III colon cancer[2,10]. Patients (n = 1886) were randomised to receive XELOX (n = 944) or 5-FU plus FA (n = 942)[10]. In the 5-FU plus FA control arm patients followed one of two treatment regimens. The Mayo clinic regimen consisted of 20 mg/m^2 FA given as a daily intravenous (IV) bolus injection with 425 mg/m^2 5-FU IV bolus injection on days 1–5 of a four-week cycle for a total of six cycles (24 weeks). The Roswell Park regimen group received 500 mg/m^2 FA, given as a two-hour IV infusion with 500 mg/m^2 5-FU IV bolus injection one hour after the start of the FA infusion on day 1 of weeks 1–6 of each eight-week cycle, for a total of four cycles (32 weeks). In the XELOX experimental arm, 1000 mg/m^2 capecitabine was administered twice daily in three-week cycles (two

weeks treatment followed by one week without) combined with 130 mg/m^2 intravenous (IV) oxaliplatin infusion over two hours on day 1 of each cycle. The XELOX treatment regimen was administered for eight cycles (24 weeks)[2,10].

The primary endpoint for this study was disease-free survival (DFS) in the intention to treat (ITT) population[2]. Secondary endpoints included safety, overall survival (OS) and relapse-free survival (RFS)[2]. Following three, four and five years of follow-up patients in the XELOX treatment arm of the ITT population had an increased DFS rate (71%, 68% and 66% respectively) and a hazard ratio (HR) of 0.80 (95% CI, 0.69-0.93; p = 0.0045), when compared with the 5-FU/FA arm (67%, 62% and 60% respectively)[2,13]. Additionally, the secondary endpoints of RFS and OS following three, four and five years of follow-up demonstrated the superiority of XELOX when compared with 5-FU/FA, although the difference in OS did not reach statistical significance (p = 0.1486)[2].

3.1.2 MOSAIC: Objectives, Design and Results

This open label, multicentre, phase III study was designed to compare the treatment effects and safety of FOLFOX-4 with 5-FU plus FA in the adjuvant treatment of colon cancer[11]. Chemotherapy-naïve patients (n = 2246) who had undergone curative resection for stage II or stage III colon cancer were randomised to one of two treatment arms[12]. The 5-FU plus FA control arm (n = 1123) comprised a two-hour infusion of 200 mg/m^2 FA followed by a bolus of 400 mg/m^2 5-FU and then a 22-hour infusion of 600 mg/m^2 5-FU given on two consecutive days every 14 days, for 12 cycles. The FOLFOX-4 experimental group (n = 1123) were treated with 5-FU and FA as specified in the control arm, along with a two-hour IV infusion of 85 mg/m^2 oxaliplatin given simultaneously with FA treatment[12].

The primary endpoint for this study was comparison of DFS in the ITT population after three years of follow-up, while the secondary endpoint was OS[11]. A subgroup analysis of patients with stage III colon cancer was considered most relevant for this submission. After three and five years follow-up the stage III patients (n = 1347) in the ITT population of the FOLFOX-4 experimental arm (n = 672) had increased DFS rates (72.2% and 66.4% respectively) when compared with patients in the 5-FU/FA group (n = 675; 65.3% and 58.9% respectively)[11,12]. The HR at five years was 0.78 (95% CI, 0.65-0.93; p = 0.005)[11]. Additionally, overall survival in patients with stage III colon cancer was increased in the FOLFOX-4 arm after six years[11].

3.1.3 Indirect comparison of the NO16968 and MOSAIC studies

Both the NO16968 and MOSAIC studies confirm that combination of oxaliplatin with fluoropyrimidine treatment is more effective than fluoropyrimidines alone as adjuvant therapies for stage III colon cancer[2]. Additionally, the studies demonstrate that both infused 5-FU/FA and capecitabine are effective in combination with oxaliplatin.

In order to allow an indirect comparison between the two studies, the company makes the assumption that the control regimens used in the NO16968 and MOSAIC studies are comparable in efficacy[2], as demonstrated in a study by the MOSAIC investigators[14]. Based on this assumption, the effects of the XELOX treatment regimen are comparable to that observed by FOLFOX-4 therapy[2]. Indeed, similar DFS rate increases and HR are observed when compared with fluoropyrimidine alone. Additionally, XELOX and FOLFOX-4 improved OS relative to fluoropyrimidine-only treatment in a similar manner. In support of these conclusions, when the FOLFOX-4 and XELOX treatment regimens were directly compared as a first line treatment for metastatic colorectal cancer, XELOX was found to be noninferior[15].

3.2 Mixed treatment comparison

Five studies were identified in order to allow the application of a network meta-analysis comparing XELOX with other treatment regimes in the adjuvant treatment of colon cancer[2]. These are described in Table 1.

Table 1: Summary of treatment regimens and colon cancer stage in the relevant studies utilised in the network meta-analysis.

Study	Stage	Comparator 1	Comparator 2
C96.1	II OR III	LV5FU2 — FA as a two-hour infusion of dl- or l-leucovorin (200 or 100 mg/m^2 respectively), followed by bolus 5-FU 400 mg/m^2 and a 22-hour infusion of 5-FU 600 mg/m^2 for two consecutive days every 14 days[14,16].	FULV — FA as a 15 minute infusion of dl- or l-leucovorin (200 or 100 mg/m^2, respectively), followed by bolus 5-FU 400 mg/m^2 for five consecutive days every 28 days[14,16].
MOSAIC	II OR III	FOLFOX-4 — FA 200 mg/m^2 as a two-hour infusion, followed by bolus 5-FU 400 mg/m^2 and a 22-hour infusion of 5-FU 600 mg/m^2 for two consecutive days every 14 days, plus a two-hour infusion of 85 mg/m^2 of oxaliplatin on day 1, given simultaneously with FA[12].	LV5FU2 — two-hour infusion of 200 mg/m^2 FA followed by bolus 5-FU 400 mg/m^2 and then 22-hour infusion of 600 mg/m^2 5-FU for two consecutive days every 14 days[12].
X-ACT	III	Capecitabine monotherapy — oral capecitabine 1250 mg/m^2 twice daily on days 1–14 every 21 days[17].	FULV — Rapid infusion of 20 mg/m^2 FA followed by IV bolus of 5-FU at 425 mg/m^2 on days 1–5 every 28 days[17].
C.07	II OR III	FLOX — two-hour IV infusion 500 mg/m^2 FA plus 500 mg/m^2 IV bolus of 5-FU given weekly for six weeks followed by a two week rest period. Additionally, 85 mg/m^2 of oxaliplatin was administered as a two hour infusion before FA and 5-FU on weeks 1, 3 and 5[18].	FULV — two-hour IV infusion 500 mg/m^2 of FA. 5-FU 500 mg/m^2 was administered as an IV bolus one hour after FA infusion begun and was administered weekly for six weeks, followed by a two week rest period[18].
NO16968	III	XELOX — two-hour IV infusion of oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1000 mg/m^2 given twice daily for 14 days of a three week cycle[10].	FULV — given as one of two regimens: Mayo Clinic regimen: rapid IV infusion of FA 20 mg/m^2 followed by IV bolus of 5-FU 425 mg/m^2 on days 1–5 of a four-week cycle. Roswell Park regimen: two-hour IV infusion of FA 500 mg/m^2 plus IV bolus injection of 5-FU 500 mg/m^2 on day 1 of weeks 1–6 of an eight-week cycle[10].

Median HRs were calculated using the networked meta-analysis methodology outlined in the company submission. These were used to compare treatment between studies.

Table 2: Median hazard ratios and 95% credible intervals obtained from the networked meta-analysis (compared to bolus 5-FU/FA)[2]

Treatment	Three-year DFS Hazard Ratio	Five-year OS Hazard Ratio
LV5FU2	1.04 (0.80 to 1.33)	1.02 (0.77 to 1.34)
Capecitabine	0.87 (0.75 to 1.00)	0.86 (0.74 to 1.00)
FLOX	0.81 (0.69 to 0.95)	0.88 (0.76 to 1.03)
XELOX	0.80 (0.69 to 0.93)	0.87 (0.72 to 1.05)
FOLFOX	0.80 (0.59 to 1.08)	0.86 (0.61 to 1.18)

The data obtained from this approach is summarised in Table 2 and suggests that the 5-FU and FA combination therapies, such as LV5FU2 and FULV, produce similar benefits in terms of DFS and five-year OS in colon cancer patients. Furthermore, the data suggests that regimens containing oxaliplatin (such as XELOX, FOLFOX and FLOX) result in a comparable degree of benefit in terms of DFS and OS when compared with 5-FU/FA therapies.

The data also implies that capecitabine monotherapy and oxaliplatin-containing combinations produce comparable benefits in terms of five year OS; the company state that it is unclear whether this is a genuine effect or an aberration introduced by the cross-trial methodology.

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

Many aspects of the safety profile of XELOX when compared with 5-FU/FA treatment are similar to that of capecitabine monotherapy, as observed during the X-ACT study[10,17,19]. XELOX treatment induced increases in the occurrence of hand-foot syndrome, including grade 3 events, which are similar to that observed in patients treated with capecitabine monotherapy. Comparable reductions in grade 3–4 neutropenia and stomatitis were also observed in patients treated with XELOX. Additionally, there was little evidence that treatment-related mortality was changed by treatment with XELOX or capecitabine monotherapy when compared with 5-FU/FA treatment. However, neurosensory toxicity, including grade 3–4 events, was increased in the XELOX treatment arm when compared with 5-FU/FA, which was not observed during capecitabine monotherapy. Neurosensory toxicity is commonly observed during oxaliplatin treatment; however exacerbation by capecitabine treatment cannot be excluded[1].

Withdrawal due to adverse events in the XELOX treatment arm of the NO16968 study was found to be 22%, compared with 9% in the 5-FU/FA arm[10]. This is in contrast to the X-ACT study, where the withdrawal rate was 12% in the capecitabine monotherapy treatment arm and 8% in the 5-FU/FA group[19].

In the indirect comparison of XELOX and FOLFOX-4, described in section 3.1, XELOX is associated with more hand-foot syndrome and potentially slightly more severe diarrhoea[2,10,12]. However, patients receiving XELOX treatment exhibited less stomatitis and myelotoxicity, resulting in less neutropenia, thrombocytopenia, anaemia and febrile neutropenia. Neurotoxicity in the form of sensory neuropathy appears to be comparable between FOLFOX and XELOX[10,12], indicating that the effect is potentially mediated by oxaliplatin[2].

In addition to this being an indirect comparison, there is a disadvantage that description, grading and aggregation of reactions would not be identical between studies, as the MOSAIC trial graded events according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 1.0[12] while the NO16968 study used NCI-CTC version 3.0[2,10].

In support of the conclusions drawn using this indirect comparison, the direct comparison of FOLFOX and XELOX in metastatic colorectal cancer[2] made similar observations regarding the safety profiles of these treatments[15]. This study also demonstrated that the rate of withdrawal due to adverse events was comparable for FOLFOX and XELOX (25% and 26% respectively)[15], which puts into context the observed rate of withdrawal for the XELOX treatment arm in the NO16968 trial[10].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Of the FOLFOX treatment regimens, only FOLFOX-4 has been examined in a large randomised controlled trial in the adjuvant setting, and is therefore the chosen comparator[2]. However, the company assert that the treatment regimen most likely to be used in Wales is FOLFOX-6, which entails infusion of 100 mg/m^2 oxaliplatin with 400 mg/m^2 FA as a two-hour infusion on day 1, followed by 5-FU given as bolus 400 mg/m^2 and 2300–3000 mg/m^2 given as a 46-hour continuous infusion on day 1 so that it requires one less visit to hospital for chemotherapy delivery[20].
- Studies included in the network meta-analysis recruited patients with colon and high rectum cancers[14] in addition to both stage II and stage III colon cancer[2], which is not within the scope of this appraisal. The company states that studies C96.1[16] and C.07[18] did not separately report data for the DFS HR at three years for stage III participants[2]. Although the MOSAIC trial reports DFS HR at three years for patients with stage III colon cancer, the data for combined stage II and stage III colon cancer patients is used in the meta-analysis[2].
- Furthermore, in the meta-analysis, the wide 95% credible intervals surrounding the median HR comparing the FOLFOX-4 and XELOX treatment regimens are compatible with a large reduction or increase in DFS and OS. The network meta-analysis uses median, rather than mean, HRs. The submission suggests that its use is due to the skewed distribution of the HR.
- XELOX treatment requires patients to attend hospital once every three weeks for an IV infusion of oxaliplatin followed by 14 days of capecitabine self-administered twice daily[2]. Consequently, permanent venous access is not mandatory for all patients receiving XELOX, as it is for patients receiving FOLFOX, which has an associated risk of complications. Additionally, patients do not have to attend hospital as often.
- Market research conducted by the company amongst UK oncologists as part of this submission indicates that 30% of non-trial patients with stage III colon cancer who are using adjuvant chemotherapy are receiving XELOX, which the company suggests is due to the benefits to both the patient and the NHS[2].
- Approximately 70% of patients with colon cancer are greater than 65 years of age[7]. Similar to the MOSAIC trial the median age of patients recruited into the NO16968 study was 61 and 62 years of age for the XELOX and 5-FU/FA respectively[10]. It should be noted that grade 3–4 adverse events were greater in older populations receiving XELOX when compared with younger patients. Furthermore, ESMO guidelines suggest caution in the use of novel drugs, such as oxaliplatin, for the adjuvant treatment of elderly patients; oxaliplatin is a component of both the XELOX and FOLFOX treatment regimens. However, in the NICE Technology Appraisal of capecitabine (monotherapy) and oxaliplatin, it was decided that benefits, tolerability and cost-effectiveness would be comparable in an older population[4].

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

6.1.1 Context

The company submission describes cost minimisation analyses (CMAs) of the XELOX regimen compared against the FOLFOX-4 and FOLFOX-6 regimens as adjuvant treatment following surgery in patients with stage III colon cancer[2]. The company suggests that FOLFOX-6 is the most common FOLFOX regimen used in this population in the UK[2].

There are no direct comparative trial data for the XELOX and FOLFOX regimens in this population. Therefore, an indirect unadjusted comparison of data from the pivotal trial of the XELOX regimen against bolus 5-FU/FA (trial NO16968) and a key trial of FOLFOX-4 against infused 5-FU/FA (MOSAIC) informs the CMA. In addition, the company has reported the results of a network mixed treatment comparison, which permits adjusted estimates of XELOX and FOLFOX-4 against common comparators. The company has concluded from both comparisons that there are no clinically meaningful differences between XELOX and FOLFOX-4 in terms of efficacy as measured by DFS and OS. See Appendix 1 for further details.

6.1.2 Results

The results of the base-case CMA as presented in the company submission are displayed in Table 3. Treatment with the XELOX regimen is estimated to be around £5,450 less expensive per patient compared with FOLFOX-6, and £8,750 less expensive compared with FOLFOX-4, based on the dose intensities and number of treatment cycles reportedly observed in trial NO16968 and the MOSAIC trial. The main driver of the cost differences relate to the requirement for central venous access and more costly preparation and administration for the infusions involved in the FOLFOX regimens.

Table 3: Company-reported total costs of treatment per patient[2]

	XELOX	FOLFOX-6	FOLFOX-4
Capecitabine / 5-FU	£1,263	£641	£413
Folinic Acid		£1,731	£1,731
Oxaliplatin	£4,110	£4,480	£3,808
Sub-total drug regimen costs	**£5,373**	**£6,852**	**£5,952**
Central venous access device	-	£505	£505
Pharmacy preparation	£385	£1,868	£3,268
Administration	£1,859	£3,822	£6,609
Sub-total administration costs	**£2,244**	**£6,195**	**£10,382**
Adverse events (grade 3/4)	£86	£113	£113
Total Direct Costs	**£7,703**	**£13,160**	**£16,449**

One-way sensitivity analyses explore variation in parameter estimates in the range +/-40%. The model was most sensitive to pharmacy-related costs for both FOLFOX comparisons, followed by administration costs on day 2 when comparing XELOX against FOLFOX-4. In all scenarios explored, including a worst-case scenario and drug dosing on a per protocol basis (i.e. 100% dose intensity), treatment with XELOX was reportedly less expensive by a margin of at least £3,400 per patient treated.

6.1.3 WMP critique of the company's economic evidence

Strengths of the economic evidence include:

- In the absence of direct comparative data for the XELOX regimen and FOLFOX regimens the company has made efforts to provide relevant data to inform indirect comparisons.

Limitations of the economic evidence include:

- There is a lack of direct comparative data to inform relative treatment outcomes. The CMA has been conducted on the assumption of equivalence between XELOX and FOLFOX, and is essentially based on an unadjusted indirect treatment comparison, which is prone to error and bias. An adjusted indirect comparison has also been provided to support this assumption of equivalence but also has limitations (see Appendix 1).
- The different administration routes and schedules, and adverse drug reaction profiles and incidences have the potential to impact upon patient preference, convenience and health-related quality of life, which are not captured within the CMA framework.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have identified a published cost minimisation analysis of XELOX compared against FOLFOX-6 in the adjuvant treatment of colorectal cancer, undertaken in a Greek healthcare setting[21]. It is not possible to compare the magnitude of differences in acquisition and other direct costs observed in the published analysis and the current analysis, due to inherent differences in the health care settings. However, as in the current analysis, the total costs of treatment with XELOX were lower than with FOLFOX-6, driven by lower administration and hospital costs associated with XELOX treatment.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and Methods

The company estimates there are 1,367 colon cancer cases diagnosed in Wales each year, based on 2008 incidence rates obtained from Welsh Cancer Intelligence & Surveillance Unit (WCISU) and 2009 population estimates.

Based on epidemiology data presented in a Health Technology Assessment report of oxaliplatin plus 5-FU and capecitabine (monotherapy) in the adjuvant treatment of colon cancer[22], it is estimated that 26% of patients have stage III colon cancer, and that 85% of these receive adjuvant treatment (302 patients). Company-conducted market research data is used to estimate that 55% of stage III colon cancer patients receive adjuvant chemotherapy with oxaliplatin-containing regimens (166 patients)[2]. The company considers this to be the eligible patient population for treatment with capecitabine given within the XELOX regimen. Furthermore, 55% of these patients are estimated to be already receiving XELOX[2].

7.1.2 Results

On the basis that XELOX is already being used in a majority of eligible patients, the company has assumed that positive guidance from the All Wales Medicines Strategy Group (AWMSG) would result in only a nominal budget impact. Assuming that current FOLFOX treatment is being provided as the FOLFOX-6 regimen, and taking the total direct costs per patient estimated in section 6, if the remaining 45% of patients were to switch from FOLFOX-6 to XELOX the company estimates a total cost saving of around £408,000 per annum, of which around £111,000 would be due to drug acquisition cost savings[2].

The company also notes that negative guidance would potentially shift the 55% of patients already taking XELOX to FOLFOX-6, which would increase overall costs by almost £500,000 per year.

7.1.3 WMP critique of the company's budget impact estimates

The company assumes patient numbers will remain static, although WCISU up to 2008 indicates an increase in incident cases over time[23]. As costing data are drawn from the CMA described in section 6 and Appendix 1, the limitations of the CMA are applicable to the budget impact analysis.

7.2 Comparative unit costs

Table 4 provides example drug acquisition costs for treatment with XELOX, FOLFOX-6 and FOLFOX-4, assuming a patient body surface area of 1.81m^2 (as per the pivotal trial of XELOX, study NO16968), 100% dose intensity, and an assumption of no vial wastage. British National Formulary (BNF)[24] list prices have been used to estimate mean costs per mg of each component drug. Note that there are significant further pharmacy and administration costs involved in the delivery of these regimens, which are not included in Table 4.

Table 4: Example acquisition costs for XELOX and FOLFOX regimens

Drug regimen	Cost per cycle	Cost per course
XELOX: Oxaliplatin 130 mg/m^2 IV on day 1 + capecitabine 1000 mg/m^2 twice daily orally on days 1–14 of a 3 week cycle	£930	£7,440 (based on 8 x 3-week cycles)
FOLFOX-6: Oxaliplatin 100mg/m^2 IV + Folinic acid 400 mg/m^2 IV + 5-FU 400 mg/m^2 IV bolus + 5-FU 2700 mg/m^2 IV infusion over 46 hours over day 1 and 2 of a 2 week cycle	£816	£9,792 (based on 12 x 2-week cycles)
FOLFOX-4: Oxaliplatin 85 mg/m^2 IV + Folinic acid 200 mg/m^2 IV + 5-FU 400 mg/m^2 IV bolus + 5-FU 600 mg/m^2 IV infusion over 22 hours on day 1, and Folinic acid 200 mg/m^2 IV + 5-FU 600 mg/m^2 IV infusion over 22 hours on day 2 of a 2 week cycle	£709	£8,504 (based on 12 x 2-week cycles)
This table does not imply therapeutic equivalence of the drugs or doses. See the individual Summaries of Product Characteristics and BNF for recommendations. All costs calculated from BNF list prices[24] on a per mg basis, assuming no vial wastage. Table excludes significant pharmacy and administration costs.		

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that capecitabine in combination with oxaliplatin is not suitable for shared care within NHS Wales. Capecitabine should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic agents.

8.2 Ongoing Studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6-12 months.

GLOSSARY

Disease-free survival (DFS): Time from randomisation to first occurrence of relapse of original colon cancer, development of new cancer of the colon or rectum or death due to any cause[2].

Overall survival (OS): Time from randomisation to death from any cause or last date patient known to be alive[2].

Relapse-free survival (RFS): Time from randomisation to recurrence of original cancer, development of new cancer of the colon or rectum or death due to treatment, original colon cancer or new cancer of the colon or rectum[2].

Colon cancer staging: The stages of colon cancer are defined in ESMO guidance as follows:[7]

Stage	Classification
Stage 0	Carcinoma in situ: intraepithelial or invasion of the lamina propria
Stage I (equivalent to Dukes' Stage A)	Tumour invades submucosa or muscularis propria
Stage IIA	Tumour invades through the muscularis propria into the subserosa, or into the nonperitonealized pericolic tissues
Stage IIB (equivalent to Dukes' Stage B)	Tumour directly invades other organs or structures and/or perforates the visceral peritoneum
Stage III (equivalent to Dukes' Stage C)	Metastases in regional lymph nodes
Stage 4	Distant metastases

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Appendix 1: Additional health economic analysis information

Table 1A: Health economic analysis detail[2]

Base Case Model		Appropriate?
Comparator(s)	Capecitabine in combination with oxaliplatin (as the XELOX regimen) is compared against 5-FU/FA in combination with oxaliplatin (as FOLFOX-4 and as FOLFOX-6) as adjuvant treatment following surgery for stage III colon cancer.	Yes, as requested by WMP. The company suggests that FOLFOX-6 is currently the most common FOLFOX regimen used for adjuvant treatment in this patient group in the UK[2].
Population	Chemotherapy-naive adult patients post surgery.	Yes, the modelled population reflects the licensed indication.
Analysis type	Cost minimisation analysis (CMA).	CMA approach assumes equivalence in all domains of health outcomes. There is no direct evidence of equivalence between XELOX and FOLFOX regimens.
Perspective	Considers direct medical costs only, from the perspective of NHS Wales	Yes.
Time Horizon	Costs assessed over the duration of adjuvant treatment only. Beyond this, all costs are assumed to be the same.	Appropriate if the CMA approach is considered appropriate.
Discount rate	No discounting applied	Yes, due to the short time horizon of analysis.
Efficacy	In the absence of direct comparative data, indirect unadjusted comparisons of data from the NO16968 trial of XELOX against bolus 5-FU/FA and the MOSAIC trial of FOLFOX-4 against infused 5-FU/FA have been made. In addition, the company has conducted a network mixed treatment comparison of trial data identified from a systematic review, which permits adjusted indirect comparisons to be made against and across common comparator regimens for the adjuvant treatment of stage II or III (Dukes' stage B or C) colon cancer. The company has concluded that these comparisons indicate equivalent efficacy of XELOX and FOLFOX-4 in terms of disease-free survival and overall survival. Further reference is made to the comparable efficacy of XELOX and FOLFOX demonstrated in trials in patients with advanced metastatic colon cancer.	In the absence of direct comparative data, the approach adopted by the company to demonstrate relative efficacy seems appropriate. There are inherent limitations with indirect treatment comparisons, especially unadjusted comparisons. The network mixed treatment comparison permits adjusted indirect comparisons to be made, although this included trials in patients with stage II disease in addition to patients with stage III disease. Median (rather than mean) HRs of around 1.0 for 3-year disease-free and 5-year overall survival have been reported for the indirect comparison of FOLFOX and XELOX. However, the 95% credible intervals around these estimates are wide, compatible with a 30-40% improvement or reduction in disease-free and overall survival for XELOX versus FOLFOX. This may reflect the paucity of the data available for comparative purposes. Trials of FOLFOX-6 regimen are not discussed and it is assumed that FOLFOX-6 and FOLFOX-4 are equally effective, and hence XELOX and FOLFOX-6 are assumed to be equally effective. Treatment durations are all assumed from the XELOX trial NO16968.

Table 1A. Continued

Base Case Model		Appropriate?
Adverse effects	Treatment related grade 3 or 4 adverse events with a difference in incidence of 3% or more between FOLFOX-4 arm of the MOSAIC study and the XELOX arm of NO16968 were included. Adverse events for FOLFOX-6 are assumed to be the same as for FOLFOX-4.	Appropriate adverse events (anaemia, diarrhoea, hand-foot syndrome, neutropenia) appear to have been considered in the cost analysis, but their impact on health-related quality of life, which is likely to differ between treatment regimens, is not considered in the CMA.
Utility values	Not applicable to CMA.	Appropriate if CMA approach is accepted.
Resource use	Relates to drug acquisition costs, administration costs, pharmacy and monitoring, treatment of adverse events, and patient transportation costs. Drug costs based on assumed body surface area of patients in the NO16968 trial of XELOX and the protocol-specified dose per cycle, relative dose intensities and number of cycles per course of treatment observed in the NO16968 trial for XELOX and MOSAIC trial for FOLFOX-4 (assumed same for FOLFOX-6). [NO16968: dose intensities 84% to 87% reported for XELOX components, mean of 6.7 cycles completed out of protocol-specified 8 cycles MOSAIC: dose intensities 77% to 83% reported for FOLFOX-4 components, mean of 10.7 cycles out of protocol-specified 12 cycles]	Appropriate items of resource use appear to be considered. It is assumed that all FOLFOX recipients would receive continuous infusions via central venous access device, with infusions delivered via elastomeric balloon pump, which permits patients to return home and attend hospital as a day case rather than requiring overnight hospital stay. Patient transportation costs assumed for 30% of patients based on expert opinion in relation to metastatic colon cancer, which is assumed to be applicable to the adjuvant setting. As FOLFOX treatment requires a greater number of attendances at hospital for administration, transportation costs would be increased compared with XELOX treatment. Sensitivity analysis has explored the impact of assuming no patients require transportation.

Table 1A. Continued

Base Case Model		Appropriate?
Unit costs	Direct medical costs of drugs are based on BNF list prices, with other costs reportedly based on previous HTAs in other disease areas, published unit cost data and the literature	Drug acquisition costs are calculated on a per mg basis, which does not take into account potential vial wastage for those components of the regimens delivered via the IV route.
Model Provided?	Yes	-
5-FU/FA: 5-fluorouracil and folinic acid combination treatment; BNF: British National Formulary; CMA: cost minimisation analysis; FOLFOX: infusional 5-FU in combination with FA and oxaliplatin; HR: hazard ratio; HTA: Health Technology Assessment; WMP: Welsh Medicines Partnership; XELOX: capecitabine and oxaliplatin combination therapy.		