NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Capecitabine for the treatment of advanced gastric cancer

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- health-related quality of life data from the trials
- additional data on safety, efficacy and the patient population
- additional information on current UK practice and the treatment pathway
- details of chemotherapy cycles used in the trials and alternative regimens used in routine clinical practice
- details of the statistical methodology used in the meta-analysis that combined individual patient data
- additional information on costs associated with adverse events and care during the additional survival of people on capecitabine therapy

Licensed indication

Capecitabine (Xeloda, Roche Products) is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider the results of the REAL-2 trial to be generalisable to the licensed indication of capecitabine (that is advanced gastric cancer), given that a large proportion of the people in this trial had advanced cancer of the oesophagus or the gastro-oesophageal junction?
- Does the Committee consider the results of the REAL-2 and ML17032 trials to be generalisable to people with advanced, inoperable gastric cancer in the UK?
  - People in both trials were younger – median age 63 years in REAL-2 and 58 years in ML17032 compared with a median age at death of 80 years in clinical practice.
  - The duration and dosage regimen of capecitabine used in the ML17032 trial was shorter and higher compared with that used in clinical practice.
  - A minority of people had a different histological type of cancer and this number varied more in REAL-2 compared with ML17032. This was because people recruited to REAL-2 had carcinoma of the oesophagus, oesophageal-gastric junction or stomach compared with gastric adenocarcimona in ML17032.

Cost effectiveness

- Does the Committee consider cost-minimisation analysis to be an appropriate approach to the economic evaluation of capecitabine compared with 5-FU?
- Does the Committee consider the number of treatment cycles (5.5) used in the model to be representative of UK clinical practice?

1 Decision problem

The scope restricted the eligible population to people with advanced inoperable gastric cancer as agreed at the scoping workshop. The term 'inoperable' is commonly used to differentiate patients that can be given treatment with a curative intent from those that will follow a pathway of advanced treatment that is palliative in nature.

1.1 Decision problem approach in the manufacturer's submission

Population	People with advanced, inoperable gastric cancer
Intervention	Capecitabine in combination with platinum-based chemotherapy regimens: • Epirubicin/Cisplatin/Capecitabine (ECX) regime: the capecitabine dosage is 625 mg/m^2 twice daily on days 1–21 • Epirubicin/Oxaliplatin/Capecitabine (EOX) regime: the capecitabine dosage is 625 mg/m^2 twice daily on days 1–21 • Cisplatin/Capecitabine (CX) regime: the capecitabine dosage is given on an intermittent schedule at a dose of 1000 mg/m^2 twice daily for 14 days in every 21 days; treatment continues until disease progression or intolerable toxicity
Comparators	Fluorouracil in combination with platinum-based chemotherapy regimens: • Epirubicin/Cisplatin/Fluorouracil (ECF) regime: the fluorouracil dosage is 200 mg/m^2 daily on days 1–21, as a continuous infusion. • Epirubicin/Oxaliplatin/Fluorouracil (EOF) regime: the fluorouracil dosage is 200 mg/m^2 daily on days 1–21, as a continuous infusion • Cisplatin/Fluorouracil (CF) regime: the fluorouracil dosage is 800 mg/m^2 on days 1–5 of a 21-day cycle, as a continuous infusion
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects • Health-related quality of life
Economic evaluation	A cost-minimisation approach to the economic analysis was considered more appropriate and has been used in the submission. This is because both trials considered in the submission looked for, and demonstrated non-inferiority of clinical outcomes between capecitabine and 5FU. Costs are considered from an NHS and personal social services perspective

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that both trials included people with advanced gastric cancer with an average age that was lower than that normally seen in clinical practice. The ERG also noted that REAL-2 included a large number of people with advanced cancer of the oesophagus or the gastro-oesophageal junction whereas the licensed indication for capecitabine is advanced gastric cancer. However, the ERG's clinical advisor felt that this was not an issue because the tumour site did not change the effects of treatment.

1.2.2 Intervention

The ERG noted that the regimens used in the trials were consistent with those used in UK clinical practice. However, they noted that the dosages and duration used in the CX regimen were not representative of UK clinical practice.

1.2.3 Comparators

The ERG considered the comparators used by the manufacturer to be appropriate. They noted, however, that in clinical practice the dosages used in the CF regimen would be lower than those presented by the manufacturer.

1.2.4 Outcomes

The ERG noted that the outcomes presented by the manufacturer were clinically relevant, but considered the limited reporting of quality-of-life data to be a major weakness.

1.2.5 Other issues

The ERG highlighted that frailer people may not withstand the standard dosages of triple combination chemotherapy regimens used in the manufacturer's submission.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The key clinical evidence in the submission came from two phase III multicentre randomised controlled trials (ML17032 and REAL-2). These trials assessed the non-inferiority of capecitabine compared with fluorouracil (5-FU) for the treatment of advanced gastric cancer. REAL-2 compared ECX and EOX combinations with ECF and EOF combinations. ML7032 compared CX with CF combination. A summary of the trials is given in table 1. For more details, please refer to pages 28–36 of the manufacturer's submission.

Table 1 Summary of capecitabine trials (pages 29–31 of the manufacturer's submission)

Trial name	Design and duration	Participants	Intervention and comparator	Outcomes
REAL-2	17 months Phase III randomised controlled trial UK multicentre	Adults with unidimensionally measurable, histologically verified locally advanced or metastatic adenocarcinoma, squamous cell or undifferentiated carcinoma of the oesophagus, oesophagogastric junction or stomach. Primary tumour classified as inoperable either at laparatomy or by CT scan and endoscopic ultrasound results and ECOG PS of 0–2	**ECX (n = 241)** Epirubicin 50 mg/m^2 IV, day 1; Cisplatin 60 mg/m^2 IV day 1; Capecitabine 625 mg/m^2 orally twice daily, days 1–21 **ECF (control arm) (n = 249)** Epirubicin 50 mg/m^2 IV, day 1; Cisplatin 60 mg/m^2 IV, day 1; 5-FU 200 mg/m^2 IV days 1–21 as a continuous infusion via a central line **EOX (n = 239)** Epirubicin 50 mg/m^2 IV, day 1; Oxaliplatin 130 mg/m^2 IV, day 1; Capecitabine 625 mg/m^2 orally twice daily, days 1–21 **EOF (n = 235)** Epirubicin 50 mg/m^2 IV, day 1; Oxaliplatin 130 mg/m^2 IV, day 1; 5-FU 200 mg/m^2 IV, days 1–21 as a continuous infusion via a central line In all cases treatment was repeated every 3 weeks for 8 cycles in the	**Primary endpoint** Non-inferiority of overall survival in people receiving capecitabine compared with those receiving 5-FU Non-inferiority of overall survival in people receiving oxaliplatin compared with those receiving cisplatin **Secondary endpoints** Non-inferiority of progression-free survival Response rates Duration of response and time to progression Toxicity Quality of life

			absence of progressive disease or unacceptable toxicity	
ML 17032	22 months Phase III randomised controlled trial Multicentre	Adults with histologically confirmed gastric adenocarcinoma with advanced and/or metastatic disease; at least one measurable lesion according to RECIST that had not been irradiated and a Karnofsky PS of ≥70%	**CX (n = 160)** Cisplatin 80 mg/m^2 IV, day 1; capecitabine 1000 mg/m^2 orally, twice daily, days 1–14 **CF (control arm) (n = 156)** Cisplatin 80 mg/m^2 IV, day 1; 5-FU 800 mg/m^2 IV, days 1–5 as a continuous infusion	**Primary endpoint** Non-inferiority of progression-free survival **Secondary endpoints** Non-inferiority of overall survival Time to disease progression Duration of response Time to response Overall RR Complete RR

CF: cisplatin plus fluorouracil; CX: cisplatin plus capecitabine; ECF: epirubicin plus cisplatin and fluorouracil; ECOG: Eastern Cooperative Oncology Group; ECX: epirubicin plus cisplatin and capecitabine; EOF: epirubicin plus oxaliplatin and fluorouracil; EOX: epirubicin plus oxaliplatin and capecitabine; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumours; RR: response rate

REAL-2 trial

The REAL-2 trial was designed to demonstrate two primary endpoints:

- overall survival in people receiving capecitabine is non-inferior to those receiving 5-FU and
- overall survival in people receiving oxaliplatin is non-inferior to those receiving cisplatin.

Results of the 2 × 2 comparisons and of individual regimens are shown in table 2, although the study was not powered to detect differences in the individual comparisons. The manufacturer reported that REAL-2 found statistically significant non-inferiority of overall survival for capecitabine using a hazard ratio (HR) adjusted for performance status, extent of disease and age (HR 0.89; 95% confidence interval [CI] 0.77 to 1.02) in the per-protocol population. This was based on the comparison [ECF+EOF] versus [ECX+EOX].

The manufacturer also reported that for the secondary endpoints, there was no significant difference in progression-free survival between the capecitabine and the 5-FU arms or between the cisplatin and the oxaliplatin arms. However, the trial showed a non-significant trend favouring capecitabine over

5–FU and oxaliplatin over cisplatin. For further details, please see pages 42–43 of the manufacturer's submission).

Table 2 Unadjusted overall survival in REAL-2 (see page 42 of the manufacturer's submission)

Overall survival results for non-inferiority (2 × 2 comparisons) and individual regimens			
2 × 2 comparisons per protocol	**1-year overall survival (%) (95% CI)**	**Median overall survival (months)**	**HR (95% CI)**
5FU: ECF plus EOF	39.4 (35.0 to 44.0)	9.6	Reference regimen
Capecitabine: ECX plus EOX	44.6 (40.1 to 49.0)	10.9	0.86 (0.80 to 0.99)*
Cisplatin: ECF plus ECX	40.1 (35.7 to 44.4)	10.0	Reference regimen
Oxaliplatin: EOX plus EOF	43.9 (39.4 to 48.4)	10.4	0.92 (0.80 to 1.10)*
Intention-to-treat regimens			
ECF n = 263	37.7 (31.8 to 43.6)	9.9	Reference regimen
EOF n = 245	40.4 (34.2 to 46.5)	9.3	0.95 (0.79 to 1.15)
ECX n = 250	40.8 (34.7 to 46.9)	9.9	0.92 (0.76 to 1.11)
EOX n = 244	46.8 (40.4 to 52.9)	11.2	0.80 (0.66 to 0.97)†
CI: confidence interval; ECF: epirubicin plus cisplatin and fluorouracil; ECX: epirubicin plus cisplatin and capecitabine; EOF: epirubicin plus oxaliplatin and fluorouracil; EOX: epirubicin plus oxaliplatin and capecitabine; HR: hazard ratio			

*The upper limit of the 95% CI excludes 1.23 we can therefore conclude non-inferiority
†p = 0.02 on comparison with ECF.

ML 17032 trial

The primary endpoint in the ML 17032 trial was non-inferiority of progression-free survival. In the per-protocol population, there was non-inferiority of progression-free survival in people receiving CX compared with those receiving CF (adjusted HR 0.85, 95% CI 0.65–1.11, p = 0.005). The manufacturer's submission reports that the results showed a trend towards improved progression-free survival with CX compared with CF in the unadjusted analysis.

The median overall survival was 10.5 months for CX compared with 9.3 months for CF (HR 0.85, 95% CI 0.64 to1.13, p = 0.008). For more details, please refer to pages 41–42 of the manufacturer's submission.

Meta-analysis

The manufacturer also reported a published meta-analysis that combined the individual data from 1318 people taking part in the REAL-2 and ML 17032 trials. The aim of the meta-analysis was to test whether capecitabine was superior to 5-FU within the double and triple combination chemotherapy regimens for patients with advanced oesophago-gastric cancer. The primary endpoint was overall survival and the secondary endpoints were progression-free survival and response rate.

The median overall survival for the intention-to-treat population was 285 days (95% CI 265 to 305 days) for people treated with 5-FU (n = 664) and 322 days (95% CI 300 to 343 days) for people treated with capecitabine (n = 654). This resulted in an unadjusted HR of 0.87 (95% CI 0.77 to 0.98, p = 0.027) in favour of capecitabine. There was no evidence of any significant heterogeneity of treatment effect according to baseline patient characteristics. The meta-analysis reported that superiority of capecitabine over 5-FU was maintained with multivariate analyses (adjusted HR 0.87, 95% CI 0.77 to 0.98, p = 0.02). For the secondary endpoints, the meta-analysis reports an insignificant trend towards improved progression-free survival in people receiving capecitabine (unadjusted HR 0.91, 95% CI 0.81 to 1.02, p = 0.093).

Adverse events

The ML 17032 and REAL-2 trials reported that most treatment-related adverse events occurred with similar frequency in both the capecitabine and the fluorouracil arms. The REAL-2 trial also reported a statistically significant increase in grade 3 and 4 neutropenia in the ECX arm compared with the ECF arm and an increased level of fatigue in the EOF arm compared with the EOX arm.

Stomatitis occurred more frequently and with greater severity in the 5-FU arm than in the capecitabine arm in ML17032, while hand–foot syndrome was more common in people treated with capecitabine. The ML17032 trial also

reported that adverse events leading to dose modification were more common in the CX arm (62%) compared with the CF arm (48%). It reported, however, that the rates of treatment discontinuation for safety reasons were the same in both arms of the trial (18%). For more details, please refer to pages 48–52 of the manufacturer's submission.

2.2 Evidence Review Group comments

Overall, the ERG considered that the clinical effectiveness evidence presented by the manufacturer reflected the available relevant evidence. However, the ERG had the following concerns about the manufacturer's submission and the potential for bias in the REAL-2 and ML17032 trials:

- Although the ERG noted that the REAL-2 and the ML 17032 trials used appropriate outcomes, there were limited data on health-related quality of life. The ML17032 trial did not report quality of life data and in the REAL-2 trial data were limited to baseline scores and changes from baseline at 12 and 24 weeks.
- The ERG considered that the number of cycles used in the model did not represent the number used in UK clinical practice. The maximum number of cycles in clinical practice is usually six, whilst in REAL-2 the median (rather than the maximum) number of cycles received was six.
- The ERG highlighted that, in clinical practice, 5-FU and capecitabine would be administered in lower doses in the double combination chemotherapy regimen. Specifically the ERG noted that 5-FU and capecitabine would be given at lower doses for the whole duration of the 21-day cycle rather than 5 and 14 days respectively as stated in the manufacturer's submission. This regimen would be given to frailer people who could not withstand the toxicity of a triple combination chemotherapy regimen. The ERG also noted that in the EOX and EOF regimens oxaliplatin is used outside its licensed indication.

- The ERG noted that there was a lack of blinding in the two trials. The REAL-2 trial did not use an independent outcome assessment, although the primary outcome of this study was overall survival. The ERG also noted that the data for independently assessed secondary outcomes for the ML17032 trial provided by the manufacturer in response to a request from the ERG differed significantly from those provided by non-independent assessors.
- The ML17032 trial was underpowered when the analyses were altered to use a non-inferiority margin of 1.25, rather than 1.40 as originally planned.
- A meta-analysis of individual patient data presented by the manufacturer showed the efficacy of capecitabine in improving overall survival and suggested that capecitabine was superior to 5-FU. The ERG noted that there was limited reporting of the methods used in the meta-analysis. It was therefore unable to assess the validity of the results.

2.3 Statements from professional/patient groups and nominated experts

Clinical specialists noted that the current standard treatment for advanced inoperable gastric cancer is palliative chemotherapy with ECF, ECX or EOX. In people with contraindications to these regimens (for example due to pre-existing peripheral neuropathy, renal impairment or impaired left-ventricular cardiac function), a combination of carboplatin and infused 5-FU or capecitabine (Carbo-F or Carbo-X) may be used. They noted that the majority of oncologists in the UK are currently using the EOX regimen as first line-therapy; this was not in keeping with the information provided by the manufacturer on page 17 of the submission. The main alternative to capecitabine is infused 5-FU, administered using a pump connected to a central venous access device, and delivered continuously throughout treatment. They noted that the use of capecitabine in advanced oesophago-gastric cancer in clinical practice is entirely reflective of that reported in the REAL-2 trial, largely because this is a UK-based multicentre study. They

pointed out that a central venous access device is associated with an increased risk of thromboembolic and infective complications, and that oral therapy allows dose adjustments, making it easier to manage any fluoropyrimidine-related toxicity. Additionally, people prefer oral treatments. People receiving infused 5-FU through a central venous access device have to go to hospital every week for treatment whereas people receiving capecitabine only have to visit hospital once every 3 weeks. And no additional tests are required for people receiving capecitabine compared with infused 5 FU. However, people with severe renal impairment cannot be treated with capecitabine, although they can receive infused 5-FU can be used in these patients with appropriate dose adjustments.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's submission states that the economic evaluation of capecitabine is undertaken within its licensed indication for the first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Three sets of analyses were undertaken, a comparison of:

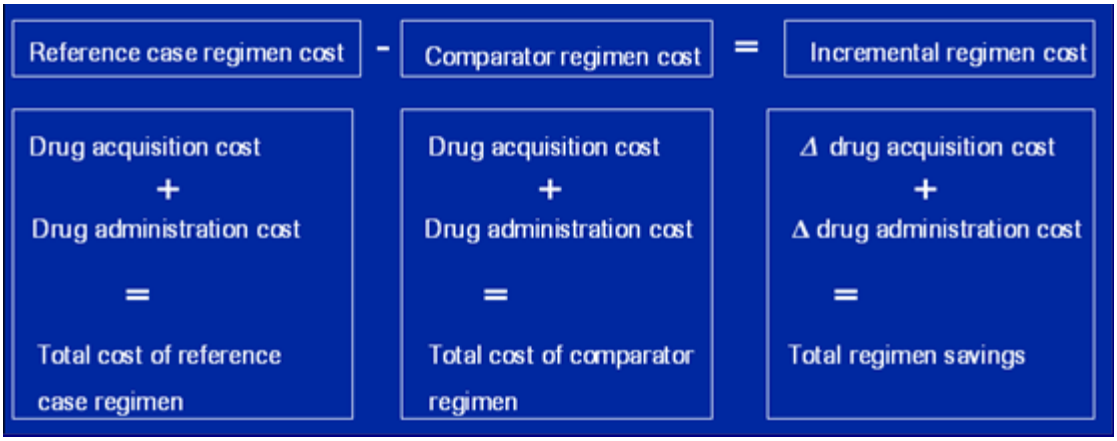
- ECX with ECF
- EOX with EOF
- CX with CF.

A total of six regimens were therefore analysed in the cost-minimisation model in the submission. The dosages in each regimen were analysed according to the summary of product characteristics for each treatment. For more details, please refer to pages 56–57 of the manufacturer's submission.

On the basis of equivalent clinical effectiveness, similar safety and improved patient convenience, a cost-minimisation model was developed to evaluate the costs for each regimen. The manufacturer reported that this captured all significant incremental direct costs relating to switching from 5-FU based

therapies to capecitabine-based therapies. The model considered both the drug acquisition and drug administration costs for all the regimens evaluated (figure 1).

Figure 1 Schematic of the cost minimisation model (see page 60 of manufacturer's submission)



The drug utilisation costs for each regimen were calculated by taking into account the licensed dose, dose intensity, mean number of cycles and body surface area. The drug administration costs for each regimen were calculated by taking into account staff costs, medical supply costs, pharmacy costs, NHS transport costs (the NHS supplies transport for 20% of people going to hospital) and hospitalisation (outpatient hospital visits and inpatient hospital stays). People entered the model at the start of treatment when they received either capecitabine or 5-FU and left the model after 5.5 cycles, which was the time horizon of the model. Because the trial results showed that there were no major differences in adverse event rates between capecitabine and 5-FU, the costs associated with management of adverse events were not included in the model. For more details, please refer to pages 60–63 of the manufacturer's submission.

Healthcare resource utilisation was estimated using a combination of sources, including clinical trial information, nurse expert opinion, previous NICE submissions, Personal Social Services Research Unit, British National Formulary and literature sources. All the drug acquisition costs for

capecitabine were discounted by 10% according to the Pharmaceutical Pricing Regulation Scheme price adjustments.

Results

The base-case results included all the drug acquisition and administration costs for all the regimens considered in the submission. No drug wastage was taken into account. All capecitabine-based regimens were shown to be cost saving compared with equivalent 5-FU-based regimens.

The total acquisition cost for ECX was £1927 compared with £1447 for ECF. The incremental drug acquisition cost for ECX compared with ECF per patient was therefore £480 (£1927 – £1447). The total drug acquisition cost for EOF was £4482 compared with £5010 for EOX. The incremental drug acquisition cost for EOX compared with EOF was therefore £528 (£5010 – £4482).

The total drug administration cost for ECX and EOX was £1719 compared with £3819 for ECF and EOF. Therefore the incremental drug administration cost for ECX compared with ECF was the same as that for EOX compared with EOF. This was £2100 (£3819 – £1719) for a mean of 5.5 treatment cycles per person.

The overall NHS cost savings for switching from 5-FU based regimens to capecitabine-based regimens are shown in tables 3 and 4. For more information, please refer to pages 89–91 of the manufacturer's submission.

Table 3 Overall NHS cost of ECF and ECX regimens (see page 91 of manufacturer's submission)

07/08 Reference costs	ECX cost (£)	ECF cost (£)	Incremental cost ECF vs ECX (£)
Drug acquisition	1927	1447	–480
Drug administration	1719	3819	2100
Total	3646	5266	
Savings			**1620**
ECF: epirubicin plus cisplatin and fluorouracil; ECX: epirubicin plus cisplatin and capecitabine			

Table 4 Overall NHS cost of EOF and EOX regimens (see page 91 of manufacturer's submission)

07/08 Reference costs	EOX cost (£)	EOF cost (£)	Incremental cost EOF vs EOX (£)
Drug acquisition	5010	4482	–528
Drug administration	1719	3819	2100
Total	6729	8301	
Savings			**1572**
EOF: epirubicin plus oxaliplatin and fluorouracil; EOX: epirubicin plus oxaliplatin and capecitabine			

For the double combination chemotherapy regimens the drug acquisition cost for CX was £1555 compared with £872 for CF. The incremental drug acquisition cost of CX compared with CF per patient was £683 (£1555 – £872). The drug administration cost for CX was £1687 compared with £6580 for CF. The incremental drug administration cost for CX compared with CF was therefore £4893 (£6580 – £1687). The overall NHS saving for switching from CF to CX is shown in table 5. For more information please refer to pages 91–92 of the manufacturer's submission.

Table 5: Overall NHS cost of CF and CX (see page 93 of the manufacturer's submission)

07/08 Reference costs	CX (£)	CF (£)	Incremental cost CF vs CX (£)
Drug acquisition	1555	872	683
Drug administration	1687	6580	–4893
Total	3242	7452	
Savings			**4210**

Sensitivity analysis

The manufacturer undertook a series of one-way sensitivity analyses to test the robustness of the results by varying most of the parameters used in the evaluation. All capecitabine-based regimens remained cost saving compared with equivalent 5-FU regimens. The manufacturer also presented a scenario

analysis in which people receiving CF regimen attended hospital as inpatients rather than outpatients. Overall NHS cost for the CF arm was £9950 compared with £3242 for the CX arm, resulting in a saving of £6708 in favour of capecitabine.

The manufacturer conducted a worst case scenario analysis in which all the parameters were made least favourable to capecitabine. The cost saving by using capecitabine instead of 5-FU was £1174. On this basis, the manufacturer concluded that undertaking a probabilistic sensitivity analysis was not necessary since the uncertainty was minimal. For more details, please refer to pages 94–96 of the manufacturer's submission.

The manufacturer undertook a threshold analysis to estimate what the gains in quality adjusted life years (QALYs) would need to be for the fluorouracil-based regimens to change the cost effectiveness in favour of 5-FU. With no utility data from the trial, a utility value of 0.73 was assigned to people with advanced gastric cancer in a progression-free health state, adopted from the BO18255 trial of people with advanced gastric cancer reported by Van Cutsem et al. (2009). The results indicated that if the maximum acceptable amount to pay for a QALY was £20,000 then ECF, EOF and CF regimens would have to gain 1.33, 1.29 and 3.46 months respectively against the equivalent capecitabine-based regimens to be cost effective. If the maximum acceptable amount to pay for a QALY was £30,000, then the gains in the fluorouracil-based regimens would have to be 0.89, 0.86 and 2.31 months respectively compared with the equivalent capecitabine-based regimens. For more details, please refer to pages 97–98 of the manufacturer's submission.

3.2 Evidence Review Group comments

Overall, the ERG considered the manufacturer's approach to the economic evaluation reasonable and that the cost-minimisation analysis used in the submission was acceptable. The ERG stated that there was minimal change

to the model when many of the assumptions used were explored. However, the ERG highlighted the following concerns:

- The ERG pointed out that treatments cannot be considered to be exactly equivalent due to uncertainty in estimating their effectiveness. By conducting a cost minimisation analysis, the manufacturer did not address the uncertainty around the estimates of efficacy.
- A full probabilistic sensitivity analysis was not performed to address the uncertainties around the costs and effects used in the model.
- The ERG was unable to reproduce the results of the worse case scenario because the manufacturer did not include this in the electronic Excel file submitted.
- The ERG noted that adverse events had not been included in the cost-minimisation model as the manufacturer assumed they were similar in the capecitabine and 5-FU arms. The ERG highlighted that rare adverse events may not have been identified because of the large sample sizes needed to detect these. Therefore, the ERG felt that some uncertainty remained about treatment-related adverse events associated with capecitabine and 5-FU regimens.

The ERG noted some additional areas of uncertainty. In the model, the manufacturer calculated capecitabine costs based on milligrams used. The ERG considered that in clinical practice, this would be rounded to match the available tablets. It also considered that in calculating 5-FU costs, wastage had not been taken into account. The ERG noted that when calculating epirubicin, cisplatin and oxaliplatin costs, the manufacturer used an average of the NHS list prices. In practice, the NHS is likely to prefer the cheapest product. The ERG also considered that, in practice, the dose of capecitabine may be reduced by 25–50% because of toxicity. For further information, please refer to pages 63–68 of the ERG report.

The ERG undertook exploratory analyses that took into account many of the above areas of uncertainty. The results are presented in table 6. In all

analyses capecitabine was cost saving compared with 5-FU. For more information, please refer to pages 70–79 of the ERG report.

Table 6 Summary of results of ERG exploratory analysis compared with the manufacturer's results (see page 79 of the ERG report)

ERG exploratory analysis and manufacturer's estimate	Incremental cost ECX vs. ECF		Incremental cost EOX vs.EOF		Incremental cost CX vs. CF	
	ERG	MS	ERG	MS	ERG	MS
Drug acquisition (£)	424	£480	£471	£528	£742	£683
Drug administration (£)	-£2,009	-£2,100	-£2,009	-£2,100	-£4,802	-£4,893
Total (£)	**-£1,585**	**-£1,620**	**-£1,538**	**-£1,572**	**-£4,060**	**-£4,210**

CF: cisplatin plus fluorouracil; CX: cisplatin plus capecitabine; ECF: epirubicin plus cisplatin and fluorouracil; ECX: epirubicin plus cisplatin and capecitabine; EOF: epirubicin plus oxaliplatin and fluorouracil; EOX: epirubicin plus oxaliplatin and capecitabine

The ERG undertook further sensitivity analyses that explored the intensity of capecitabine and all the other regimens, the number of cycles and the transport costs. The ERG also conducted an additional worst case scenario and threshold analysis of the cost of extending survival by capecitabine. The overall conclusions did not change in relation to those in the manufacturer's submission. For more details, please refer to pages 81–85 of the ERG report.

4 Authors

Raphael Yugi, Sally Doss, Rebecca Trowman, with input from the Lead Team (Dr James Moon, Olivia Wu and David Thomson).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination and Centre for Health Economics:

- Norman G, Soares M, Peura P, et al. Capecitabine for the treatment of advanced gastric cancer: a single technology appraisal, CRD, 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products

II Professional/specialist, patient/carer and other groups:

- Royal College of Physicians
- Macmillan Cancer Support