All Wales Therapeutics and Toxicology Centre
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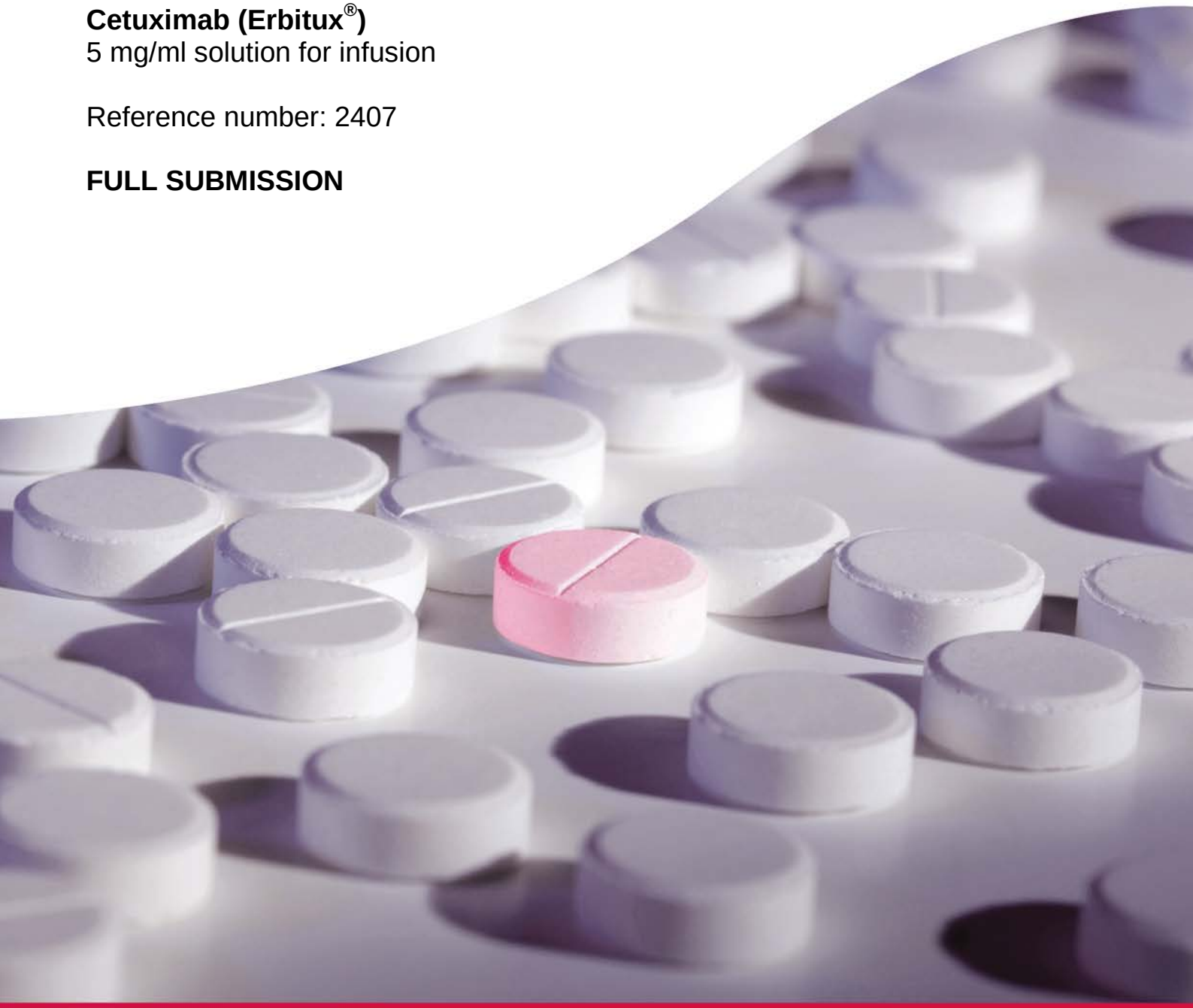
AWMSG SECRETARIAT ASSESSMENT REPORT

Cetuximab (Erbitux®)
5 mg/ml solution for infusion

Reference number: 2407

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Cetuximab (Erbitux®) 5 mg/ml solution for infusion

This assessment report is based on evidence submitted by Merck Serono Ltd on 26 May 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Cetuximab (Erbitux®) for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer • in combination with irinotecan-based chemotherapy; • in first-line in combination with FOLFOX; • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan[2].
Dosing	Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least one hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions. Cetuximab is administered once a week. The initial dose is 400 mg cetuximab per m^2 body surface area. All subsequent weekly doses are 250 mg cetuximab per m^2 each. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	The marketing authorisation was amended on 18 December 2013[3]; the indication was restricted to treatment of patients with EGFR-expressing RAS wild-type metastatic colorectal cancer. It was previously licensed for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer: in combination with chemotherapy; or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan on 23 October 2008[4].

2.0 DECISION CONTEXT

2.1 Background

Colorectal cancer originates in the lower part of the large intestine and includes cancers of the colon, rectum and appendix[5]. It is the third most common type of cancer in Wales, with 2,460 new cases being reported in 2012[6]. The incidence increased by 28.5% between 2002 and 2012. In metastatic colorectal cancer (mCRC), the tumour spreads beyond the local or regional lymph nodes to other parts of the body. At the time of diagnosis, approximately 20–55% of patients with colorectal cancer already have metastatic disease[5].

Cetuximab is an immunoglobulin G1 monoclonal antibody that specifically targets and inhibits ligand binding to the epidermal growth factor receptor (EGFR) thus preventing the proliferation of cells that require EGFR activation for growth[7,8].

Emerging data and an increased understanding of the role of predictive biomarkers for EGFR–targeted therapy has resulted in the modification of the licensed indication for

cetuximab[1]. Cetuximab was originally licensed in 2008 for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer[4]. In December 2013, the licensed indication was restricted from KRAS wild-type mCRC to RAS wild-type mCRC because of evidence supporting a strong response to treatment for this subgroup[1]. The RAS category includes patients that have both KRAS and NRAS genes (exons 2, 3 and 4). The RAS biomarker allows the identification of a patient group that is more likely to benefit from treatment with anti-EGFR therapies, such as cetuximab[1]. Evidence of RAS wild-type status is required before initiating treatment with cetuximab[2].

The applicant company has focused their submission on the use of cetuximab for first-line treatment[1]. The applicant company has not provided any evidence for the use of cetuximab as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

2.2 Comparators

The company submission focuses on the following comparators:

- Fluoropyrimidine-based chemotherapy
    - FOLFOX (folinic acid, fluorouracil, oxaliplatin)
    - FOLFIRI (folinic acid, fluorouracil, irinotecan)
- Capecitabine in combination with oxaliplatin-based therapies (CAPOX)

The applicant company submission also included a systematic literature review, network meta-analysis (NMA) and an indirect treatment comparison to identify and compare cetuximab plus fluoropyrimidine-based chemotherapies with other therapies, including bevacizumab or pantiumumab. As bevacizumab and panitumumab are not routinely used in Wales[1], these analyses are not discussed further.

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Single Technology Appraisal (TA) in progress. Colorectal cancer (metastatic) – cetuximab (review TA 176) and panitumumab (part review TA 240) (1st line). Expected publication date: April 2016[9].
- European Society for Medical Oncology (ESMO). Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2014)[10].
- NICE. TA 242. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118) (2012)[5].
- NICE. TA 176. Cetuximab for the first-line treatment of metastatic colorectal cancer (2009)[11].
- NICE. Clinical Guideline (CG) 131. Colorectal cancer: The diagnosis and management of colorectal cancer (2011)[12].
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 126. Diagnosis and management of colorectal cancer (2011)[13].
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines®). Colon cancer (2009)[14].
- NCCN. NCCN clinical practice guidelines in oncology (NCCN guidelines®). Rectal cancer (2009)[15].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a Statement of Advice for panitumumab (Vectibix®▼)[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In support of the use of cetuximab for the indication under consideration, the applicant company submission provided post-hoc subgroup analyses of RAS wild-type data from two pivotal randomised controlled trials (RCTs): CRYSTAL and OPUS[1]. When the CRYSTAL and OPUS trials were initiated, KRAS and RAS biomarkers had not yet been identified.

3.1 Clinical effectiveness studies

3.1.1 CRYSTAL

This was a phase III, multicentre, open-label RCT, which compared cetuximab plus FOLFIRI with FOLFIRI alone[1,8]. Patients with previously untreated mCRC with non-resectable metastases and an Eastern Cooperative Oncology Group (ECOG) status of ≤ 2 were eligible for trial participation. Patients continued to receive treatment until there was evidence of disease progression as assessed by computed tomography (CT) or magnetic resonance imaging (MRI), occurrence of unacceptable adverse events (AEs), or consent withdrawal[1,8].

Patients (n = 1,217) were randomised (1:1) to receive cetuximab (400 mg/m^2 administered as an initial 120-minute infusion; followed by 60-minute infusions of cetuximab [250 mg/m^2] every seven days, thereafter) and FOLFIRI (fluorouracil 400 mg/m^2 intravenous [IV] bolus followed by a 46-hour continuous IV infusion of 2,400 mg/m^2, folinic acid 400 mg/m^2 IV [racemic] or 200 mg/m^2 IV [L-form] plus irinotecan 180 mg/m^2 IV infusion, all on day one every two weeks) or FOLFIRI alone[1,8]. The retrospective post-hoc RAS wild-type subgroup analyses included 178 and 189 patients in the cetuximab and FOLFIRI and FOLFIRI groups, respectively[1].

The primary efficacy endpoint was progression free survival (PFS) in the intention to treat population (ITT; defined as the time in months from randomisation until progressive disease was first observed or death occurred due to any cause within 60 days of the last tumour assessment or randomisation). Secondary efficacy endpoints included overall survival (OS) and response rates. The addition of cetuximab to FOLFIRI significantly prolonged PFS when compared with FOLFIRI alone in the RAS wild-type subgroup (hazard ratio [HR]: 0.56; p = 0.0002) [see Table 1]). The primary endpoint was supported by secondary endpoints[1]. For median PFS in RAS wild-type, patients treated with cetuximab plus FOLFIRI progressed three months later than those treated with FOLFIRI alone. In the post-hoc RAS wild-type subgroup analyses, a median improvement of 8.2 months in OS was observed in patients that received cetuximab plus FOLFIRI when compared with FOLFIRI alone[1].

Table 1. Overview of primary and secondary endpoints for the RAS wild-type subgroup population in the CRYSTAL trial[1].

	Cetuximab plus FOLFIRI (n = 178)	FOLFIRI alone (n = 189)	p-value
Primary endpoint			
PFS			
Median PFS, months (95% CI)	11.4 (95% CI: 10.0−14.6)	8.4 (95% CI: 7.4−9.4)	p = 0.0002
Hazard ratio (95% CI)	0.56 (0.406−0.761)		–
Secondary endpoints			
OS			
Median OS, months (95% CI)	28.4 (24.7−31.6)	20.2 (17.0−24.5)	p = 0.0024
Hazard ratio (95% CI)	0.69 (0.54−0.88)		–
ORR (%) (95% CI)	66.3 (58.8−73.2)	38.6 (31.7−46.0)	p < 0.0001
DCR (%) (95% CI)	93.3 (88.5−96.5)	86.2 (80.5−90.8)	p = 0.0386

CI: confidence interval; DCR: disease control rate; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

3.1.2 OPUS

This was a phase II, multicentre, open-label RCT, comparing the efficacy and safety of cetuximab plus FOLFOX-4 with FOLFOX-4 alone in the first-line treatment of EGFR-expressing mCRC[1,7,17]. Patients with previously untreated mCRC with non-resectable metastases and an ECOG status of ≤ 2 were eligible for trial participation. Patients continued to receive treatment until there was evidence of disease progression as assessed by CT or MRI, occurrence of unacceptable AEs, or consent withdrawal[1,7,17].

Patients (n = 344) were randomised (1:1) to receive either cetuximab (400 mg/m^2 administered as an initial 120-minute infusion; followed by 60-minute infusions of cetuximab [250 mg/m^2] every seven days, thereafter) plus FOLFOX-4 (fluorouracil 400 mg/m^2 IV bolus, followed by a 22-hour continuous infusion of 600 mg/m^2 IV and folinic acid 200 mg/m^2 IV infusion on days 1 and 2, plus oxaliplatin 85 mg/m^2 IV infusion on day one, every two weeks) or FOLFOX-4 alone[1,7,17]. The retrospective post-hoc RAS wild-type subgroup analyses included 38 and 49 patients in the cetuximab plus FOLFOX-4 and FOLFOX-4 groups, respectively[1].

The primary efficacy endpoint was best overall response rate (defined as the proportion of subjects having achieved confirmed complete response [CR] or partial response [PR], as best overall response, according to radiological assessments). In the post-hoc RAS wild-type subgroup analyses, patients receiving cetuximab plus FOLFOX-4 demonstrated a superior response rate compared to those patients receiving FOLFOX-4 alone (see Table 2). The addition of cetuximab to FOLFOX-4 demonstrated clinically significant improvements in PFS and OS when compared to FOLFOX-4 alone in the RAS wild-type subgroup analyses; however, this was not statistically significant (see Table 2). For median PFS, patients treated with cetuximab plus FOLFOX-4 progressed 6.3 months later than those treated with FOLFOX-4 in RAS wild-type

subgroup analyses. A two month benefit in median OS was observed in RAS wild-type patients treated with cetuximab plus FOLFOX-4 when compared with FOLFOX-4 alone[1].

Table 2. Overview of responses for the RAS wild-type subgroup population in the OPUS trial[1].

	Cetuximab plus FOLFOX-4 (n = 38)	FOLFOX-4 alone (n = 49)	p-value
Primary endpoint			
ORR, % (95% CI)	57.9 (40.8−73.7)	28.6 (16.6−43.3)	p = 0.0084
Odds ratio (95% CI)	3.3% (1.36–8.17)		–
Secondary endpoints			
Median OS, months (95% CI)	19.8 (16.6−25.4)	17.8 (13.8−23.9)	–
Hazard ratio (95% CI)	0.94 (0.56−1.56)		p = 0.801
Median PFS, months (95% CI)	12.0 (5.8−NA)	5.8 (4.7−7.9)	–
Hazard ratio (95% CI)	0.53 (0.27−1.04)		p = 0.062
DCR, % (95% CI)	84.2 (68.8−94.0)	71.4 (56.7−83.4)	p = 0.2030

CI: confidence interval; DCR: disease control rate; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

3.2 Comparative safety

Comparative safety information was collected from the CRYSTAL and OPUS trials and analysed[1].

3.2.1 CRYSTAL

In the RAS-wild type population (n = 367), all patients in the cetuximab plus FOLFIRI group (100%; 178/178) and almost all in the FOLFIRI alone group (99%; 187/189) had at least one AE[1]. The frequencies of grade 3 and 4 AEs and serious AEs (SAEs) were consistently higher in the cetuximab plus FOLFIRI versus FOLFIRI alone groups in the RAS wild-type populations. Grade 3 and 4 AEs occurred in 144 (80.9%) patients in the cetuximab plus FOLFIRI group and 110 (58.2%) patients in the FOLFIRI alone group. The most commonly reported grade 3 and 4 AEs (occurring in ≥ 5% of patients in either group) included neutropenia (30.9% in the cetuximab plus FOLFIRI group versus 20.1% in the FOLFIRI alone group), diarrhoea (14.6% versus 9.5%) and leukopenia (8.4% versus 3.7%). Grade 3 and 4 skin reactions occurred in 21.9% versus 1.1% of patients. In the cetuximab plus FOLFIRI group, three (1.7%) patients died (one due to disease progression) and in the FOLFIRI alone group, there were five (2.6%) deaths, one of which was due to disease progression[1].

3.2.2 OPUS

In the RAS-wild type population (n = 87) all patients in the cetuximab plus FOLFOX-4 group (100%; 38/38) and all patients in the FOLFOX-4 alone group (100%; 49/49) had at least one AE[1]. The frequencies of Grade 3 and 4 AEs and SAEs were consistently higher in the cetuximab plus FOLFOX-4 versus FOLFOX-4 alone groups in the RAS wild-type population. Grade 3 and 4 AEs occurred in 30 (78.9%) patients in the cetuximab plus FOLFOX-4 group and 31 (63.3%) patients in the FOLFOX-4 alone

group. The most commonly reported grade 3 and 4 AEs included neutropenia (31.6% in the cetuximab plus FOLFOX-4 group versus 28.6% in the FOLFOX alone group) and pulmonary embolism (7.9% versus none). Grade 3 and 4 skin reactions occurred in 13.2% of patients in the cetuximab plus FOLFOX-4 group (no patients in FOLFOX-4 alone group). In the cetuximab plus FOLFOX-4 group, two (5.3%) patients died (one due to disease progression) and in the FOLFOX-4 alone group, there were three (6.1%) deaths, two of which were due to disease progression[1].

3.2 AWTTC critique

- The applicant company has focused their submission on the use of cetuximab for first-line treatment only[1]. The applicant company has not provided any evidence for the use of cetuximab as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.
- Response rates were significantly improved for cetuximab and chemotherapy than chemotherapy alone for the CRYSTAL and OPUS studies, and PFS was significantly longer for cetuximab and FOLFIRI than FOLFIRI alone[1,8,17].
- OS was significantly longer for cetuximab and FOLFIRI than FOLFIRI alone in the CRYSTAL trial only[1,8].
- At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that restricting the use of cetuximab to those patients with RAS wild-type mCRC improves the benefit without negatively affecting the risk[4].
- The efficacy data for the indication under consideration were obtained from post-hoc analyses of RAS wild-type patients from the two pivotal trials, CRYSTAL and OPUS[1]. Randomisation in the CRYSTAL and OPUS trials was not stratified by tumour mutational status, which could have resulted in imbalances between treatment groups; the RAS-wild type groups are small, particularly for the OPUS trial.
- The company highlighted that the current treatment options available for mCRC patients is somewhat limited[1]. Clinical experts contacted by AWTTC supported this view and highlighted an unmet need in this area.
- The company submission focused on the oxaliplatin- and irinotecan-based chemotherapy regimens[1]. Clinical experts have indicated that CAPOX (capecitabine and oxaliplatin) is used first-line in Wales. No comparison was provided with CAPOX.
- In the OPUS trial, a two month benefit in OS was reported in patients in the cetuximab plus FOLFOX-4 group when versus FOLFOX-4 alone group[1,17]. This would not meet the criteria in the AWMSG policy on appraising life-extending, end of life medicines[18], which states that the medicine offers an extension to life, normally of at least an additional three months, compared to current NHS treatment.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of the addition of cetuximab to FOLFOX-4 or FOLFIRI compared with each chemotherapy regimen alone as a first-line treatment for mCRC in patients with wild-type RAS status[1]. As the analyses reflect only first-line use of cetuximab in combination with chemotherapy, the economic evidence is restricted to subgroups of the full licensed indication[1].

A Markov model with a one-month cycle length has been developed. Patients in the modelled cohort start first-line treatment with FOLFOX-4 or FOLFIRI, with or without cetuximab, then either undergo curative resection of liver metastases and enter a

post-resection health state, or progress to second-line therapy (assumed to be FOLFOX-6) followed by third-line best supportive care (BSC)[1].

Progressions from first- to second-line treatment are based on post-hoc analyses of PFS data from subgroups with wild-type RAS status in the CRYSTAL trial (for the comparison with FOLFIRI) and OPUS trial (for the comparison with FOLFOX-4) (see Section 3). Progression from second- to third-line therapy is based on PFS curves obtained from the GERCOR trial of FOLFOX-6 versus FOLFIRI in chemotherapy naive patients[19], and survival in those receiving BSC is derived from retrospective analysis of a trial of the addition of cetuximab to BSC versus BSC alone in patients who had progressed on chemotherapy[20]. The proportion of patients transitioning to curative surgical resection following first-line therapy with cetuximab is derived from post-hoc analysis of CRYSTAL trial data, and is assumed to apply equally to the comparison with FOLFIRI and FOLFOX-4 in the absence of resection data from the OPUS trial. Resection rates for either FOLFIRI or FOLFOX-4 alone were obtained from the GERCOR trial[19]. Survival following resection is modelled using data from a retrospective observational study in patients with colorectal hepatic metastases rendered resectable by chemotherapy[21]. All survival data are extrapolated using parametric functions, selected on assessment of their goodness of fit to the data.

The transition probabilities derived from these data are applied equally to those who progress from first-line therapy; it is therefore implicitly assumed that any PFS benefits from the addition of cetuximab to first-line chemotherapy regimens translate directly into OS benefits. For a scenario analysis exploring cetuximab plus FOLFOX-4 compared with CAPOX, the company assumes outcomes with CAPOX will be equivalent to those with FOLFOX-4, as CAPOX data specifically in patients with wild-type RAS status to inform this comparison are lacking. The model includes grade 3 or 4 AEs of first-line treatment only, based on the frequencies observed in the CRYSTAL and OPUS trials[1].

Utility values of 0.778 for progression-free first-line, 0.769 after progression from first-line, 0.663 for third-line treatment, assessed using EQ-5D in patients with mCRC are identified in a systematic review[22,23]. For those with successful curative resection, a population average utility value (0.789) for people aged 55–64 years is assumed based on Health Survey for England data from 1996[24], and for patients with progressive disease after resection, a weighted average of second- and third-line treatment utilities (0.682), based upon the mean time spent in those health states, is assumed. Disutilities associated with AEs are assumed, based loosely on various literature sources[1].

Medicine acquisition and administration costs for chemotherapy are based on the regimens used in the CRYSTAL and OPUS trials, and are costed using British National Formulary (BNF) list prices and published unit cost data. Cetuximab acquisition costs are based on a confidential discounted price agreed in a Wales Patient Access Scheme (WPAS), and two cetuximab regimens are considered: once weekly dosing as per the licensed regimen based on the CRYSTAL and OPUS trials, and once fortnightly dosing based on company-reported standard practice in England and Wales. No vial sharing is assumed. Resource use related to AE management and health states are assumed, with liver resection resource use based on the published retrospective observational study[21] and expert opinion. RAS testing costs are included but assumed equal amongst the modelled treatment arms.

A 10-year time horizon of analysis is adopted. Costs and outcomes beyond one-year are discounted at 3.5% per annum.

4.1.2 Results

The results of the base case analyses assuming the licensed once weekly or, alternatively, fortnightly dosing of cetuximab, and a WPAS agreed confidential discount on its price, are presented in Table 3.

Table 3. Base case CUA results assuming weekly or fortnightly cetuximab dosing[1].

	Costs: weekly admin (£)	Costs: fortnightly admin (£)	LYs	QALYs	ICER: weekly admin	ICER: fortnightly admin
Cetuximab + FOLFOX-4	40,095	35,860	2.22	1.64	–	–
FOLFOX-4	26,408	26,408	1.81	1.32	–	–
Increment (cetuximab + FOLFOX-4 – FOLFOX-4)	**13,688**	**9,452**	**0.41**	**0.32**	**42,737**	**29,512**
Probability cost effective* at £20,000/QALY at £30,000/QALY	–	–	–	–	14% 33%	26% 48%
Cetuximab + FOLFIRI	42,256	37,642	2.19	1.61	–	–
FOLFIRI	27,139	27,139	1.81	1.32	–	–
Increment (cetuximab + FOLFIRI – FOLFIRI)	**15,116**	**10,503**	**0.38**	**0.29**	**51,425**	**35,731**
Probability cost effective* at £20,000/QALY at £30,000/QALY	–	–	–	–	2% 12%	9% 33%

Admin: administration; ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); LY: life-year; QALY: quality-adjusted life-year

* Probability ICER ≤ £20,000 or £30,000 per QALY gained based on probabilistic sensitivity analysis

Over a 10-year time horizon, the deterministic base case models estimate a (discounted) gain of 0.41 life years, or 0.32 quality-adjusted life years (QALYs) from the addition of cetuximab to FOLFOX-4, and a (discounted) gain of 0.38 life years, or 0.29 QALYs from the addition of cetuximab to FOLFIRI. The assumed administration regimen for cetuximab has a profound impact on the estimated incremental costs and incremental cost-effectiveness ratios (ICERs) for cetuximab; at the licensed weekly dosing regimen, the deterministic ICERs range from £42,700 to £51,400 per QALY gained, but assuming dosing on a fortnightly basis the ICERs reduce to £29,500 to £35,700 per QALY gained. Probabilistic sensitivity analyses estimate there is less than 50% probability of any of these ICER estimates falling below £30,000 per QALY gained, irrespective of the assumed dosing regimen.

The company reported one-way sensitivity analyses for the fortnightly cetuximab dosing regimen by exploring trial-based parameter estimates within the range of 95% confidence intervals. The key parameters to which the ICER estimates are most sensitive include the duration of cetuximab treatment, assumed patient body surface area, hazard ratio for progression on first-line treatment, and proportion of patients undergoing curative resection. Results of these and a scenario analysis comparing cetuximab plus FOLFOX-4 against CAPOX chemotherapy are summarised in Table 4.

Table 4. Key one-way sensitivity and scenario analyses (fortnightly cetuximab dosing) [1].

Description	ICER: cetuximab + FOLFOX versus FOLFOX	ICER: cetuximab + FOLFIRI versus FOLFIRI	Plausibility considerations
Base case analyses	£29,512	£35,731	PFS benefits of cetuximab and improved curative resection rates based on post-hoc subgroup analyses in small numbers of patients. PFS benefits of cetuximab assumed to translate into OS benefits based on modelling. Use of trial-based OS data and removal of improvement in resection rates increases ICERs to £76,284 versus FOLFOX and to £38,632 versus FOLFIRI, demonstrating sensitivity of ICER estimates to OS modelling and assumed differential in resection rates. Assumes fortnightly dosing of cetuximab. ICERs significantly greater in all analyses if assume licensed weekly dose. Unclear if RAS testing costs appropriately attributed and accrued.
95% CI for proportion on cetuximab undergoing curative resection	£24,571 to £34,748	£29,270 to £42,846	Assumed improvement in curative resection rates with cetuximab is a key driver of ICER estimates. Rates in base case based on small numbers of events in post-hoc subgroup analyses. Odds ratios based on these limited data indicate no statistically significant differences in resection rates. ICERs increase to £41,000+ versus FOLFOX and to £52,000+ versus FOLFIRI if equal resection rates assumed
95% CI for cetuximab HR for progression	n/a	£24,152 to £59,602	PFS determines OS in model and is a key driver of model estimates of ICER. As PFS based on post-hoc subgroup analyses in limited numbers of patients, uncertainty in PFS is high, and uncertainty in ICER is high.
95% CI for cetuximab treatment duration	£16,552 to £40,679	£20,764 to £49,578	Results as expected; treatment duration would influence medicine costs. Note that PFS is based on the trial data, and base case reflects trial treatment duration (approx. 24–25 weeks).
95% CI for body surface area	£19,040 to £43,040	£23,728 to £51,593	Results as expected; body surface area would influence dose requirements and hence costs of medicines.
Cetuximab + FOLFOX versus CAPOX			
Scenario analysis: CAPOX assumed same efficacy as FOLFOX	£25,861	–	No data for CAPOX specifically in RAS wild-type population – CAPOX efficacy assumed same as FOLFOX. Limitations of base case above also apply.
CI: confidence interval; HR: hazard ratio; ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); n/a: not applicable; OS: overall survival; PFS: progression-free survival			

4.1.3 AWTTC critique

The company's CUA is based on efficacy data which informed the regulatory approval of cetuximab; however, there are a number of limitations to these data and their use in the economic model.

The modelling approach implicitly assumes that improvement in PFS translates into improved OS, which is subject to uncertainty, particularly for the addition of cetuximab to FOLFOX-4. There are no direct data to inform a comparison against CAPOX, which would be a key comparator regimen in practice. Direct comparative data for the addition of cetuximab to FOLFIRI and FOLFOX-4 in the relevant patient populations are limited to post-hoc subgroup analyses in relatively small patient numbers, and the modelled ICER estimates are very sensitive to variation in the resulting parameter estimates. The company has provided analyses assuming cetuximab would be administered fortnightly based on use in practice, which significantly reduces the ICER estimates compared with the weekly administration on which the efficacy data are based. Collectively, it is uncertain that the company's base case analyses provide the best ICER estimates; it is plausible that the ICERs could exceed those reported in the base case. Analyses accounting for the joint uncertainty in parameter estimates indicate that the probability of the ICER estimates being below £30,000 per QALY is less than 50%, irrespective of the assumed administration regimen.

The company suggests that cetuximab should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[18], based on trial data showing an increase in PFS and OS when added to chemotherapy[1]. This is discussed in detail in Section 6.5.

Key strengths of the economic evidence include:

- The modelled pathway appears to be reasonable.
- The company has conducted systematic literature reviews to inform parameter values.
- Several one-way sensitivity analyses have been conducted to explore some of the key assumptions used in the base case model.

Key limitations and uncertainties in the economic evidence include:

- Direct comparative trial data with which to model the cost-effectiveness of cetuximab are limited to post-hoc subgroup analyses of the CRYSTAL and OPUS trials. These analyses were conducted in small patient numbers, particularly for the comparison against FOLFOX-4.
- Improvements in PFS with addition of cetuximab to chemotherapy, which are based on these subgroup analyses, are assumed in both base case models to translate into improved OS, which is associated with several uncertainties:
    - The CRYSTAL trial against FOLFIRI observed a significant improvement in OS; however, the OPUS trial against FOLFOX-4 observed no statistically significant difference in PFS or OS with the addition of cetuximab to FOLFOX-4 in the small subgroup of patients with wild-type RAS status. The ICER estimates are sensitive to the method of incorporating and extrapolating OS in the model, with use of trial based OS estimates potentially increasing ICER estimates (see Table 4).
- The base case models assume improvement in curative resection rates with the addition of cetuximab to chemotherapy, which is a key driver of the ICER estimates. However, the rates assumed in the model are subject to significant uncertainty, being based on small, post-hoc subgroup analyses of the CRYSTAL trial, there were no statistically significant differences in resection rates with addition of cetuximab. Removal of a difference in favour of cetuximab increases the ICER estimates significantly (see Table 4).

- The assumed administration regimen for cetuximab has a profound impact on the estimated incremental costs and cost-effectiveness of cetuximab.
    - The analyses assuming fortnightly dosing assume equivalent outcomes as for once weekly dosing.
    - One-way sensitivity analyses have been conducted only for the fortnightly dose regimen; all ICER estimates would be significantly increased with the currently licensed once weekly dose regimen.
    - It is also unclear whether RAS testing costs have been appropriately attributed and accrued in the model.
- There are no trial data to compare cetuximab against CAPOX, which is used often as a first-line regimen in clinical practice. The exploratory scenario analysis assumes CAPOX outcomes will be the same as with FOLFOX-4 in the model; however, the FOLFOX-4 data in particular have a number of limitations discussed above. The exploratory analysis of cetuximab compared with CAPOX should therefore also be interpreted with caution.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any fully published cost effectiveness analyses of cetuximab in the company's proposed positioning (as a first-line treatment for mCRC in patients with wild-type RAS status) of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company reports an incidence of colorectal cancer in 2011 of around 50 per 100,000[25]. A previous Health Technology Assessment report is quoted as providing an estimate of 52% of cases being metastatic[26]. Company-conducted market research is reported to have observed 83% of patients undergoing RAS testing[1], and of patients recruited to the FIRE-3 trial, 48.5% had RAS wild-type expressing tumours[27]. Applied to Welsh population estimates in 2011, the company estimates this equates to 322 incident cases per year meeting the licensed colorectal cancer indication for cetuximab. Of these, the company estimates 72% (232) would be sufficiently fit and eligible to receive treatment with targeted therapy. As the treatment related budget impact of cetuximab is limited to one year, it is assumed that incident cases are equivalent to prevalent cases. Projected population growth of 0.27% per year is assumed[1].

The company estimates uptake of cetuximab in combination with FOLFIRI or FOLFOX in year one to be 10% (assumed current use), rising to 70% in year five[1]. Comparators include FOLFOX-4 alone, FOLFIRI alone and CAPOX, which are assumed to be displaced in equal proportions. Treatment durations are assumed based on trial observed durations and expert opinion. Cetuximab is assumed to be dosed fortnightly, which significantly reduces administration costs compared with the licensed once weekly dosing used in the key trials[19], and its acquisition cost is based on a confidential discount price agreed via a WPAS. Other agents are costed using BNF list prices and administration costs as per the economic model in Section 4[1].

5.1.2 Results

The company estimates net budget impact in Wales in each of the next five years as in Table 5.

Table 5. Company estimates of net cost implications associated with cetuximab[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	234	234	235	235	236
Uptake (%)	10%	60%	70%	70%	70%
Treated patients	23	141	164	165	165
Net medicine acquisition cost	¶	¶	¶	¶	¶
Net administration cost	£89,599	£539,048	£630,587	£632,290	£633,997
Overall net cost	¶	¶	¶	¶	¶
¶commercial in confidence data removed					

No sensitivity or scenario analyses are provided.

5.1.3 AWTTC critique

- The company's estimates of the incidence of patients with mCRC do not accord with the actual number of incident cases registered in Wales in 2012 (2,460 cases)[6]. Consequently, the company's estimates of eligible patient numbers may be significantly underestimated, which would lead to a significant underestimation of the net budget impact of cetuximab in NHS Wales.
- Around 16.5% of the net cost estimate is a result of increased administration costs. The analysis assumes fortnightly dosing of cetuximab[1,2]. If once weekly dosing was employed, as per the clinical trials and current Summary of Product Characteristics (SPCs) recommended dosing regimen[19], administration and total net costs would be significantly increased.
- The budget impact analyses appear to assume vial sharing for all agents, which may underestimate the costs of cetuximab.
- Collectively, the budget impact estimates are subject to significant uncertainty and could plausibly be over 50% greater than those estimated by the company.

5.2 Comparative unit costs

Comparator regimens for cetuximab in combination with chemotherapy include FOLFOX-4 alone, FOLFIRI alone and CAPOX. Treatment cycles vary depending on defined regimen schedule, and different treatment exposures and intensities are to be expected due to differences in AE profiles, etc. Therefore, Table 6 provides only a pragmatic, illustrative example of comparative costs, based on BNF list prices, and approximate treatment durations assumed by the company in its CUA analysis (which are informed by trial durations and company-sought expert opinion, and average around 25 weeks for cetuximab + chemotherapy regimens), for an adult of 1.8 m^2, assuming 100% dose intensity and vial sharing, using BNF list prices[28]. RAS wild-type testing and pre-medication costs are not included.

Table 6. Example comparative medicine acquisition costs per adult of 1.8 m^2.

Regimens	Doses and treatment schedules	Cycles per year	Approximate regimen costs
Cetuximab + FOLFIRI	**cetuximab** 400mg/m^2 IV for first dose, then 250 mg/m^2 thereafter, D1 and D8 **irinotecan** 180 mg/m^2 IV, D1 **folinic acid** 400 mg/m^2 IV, D1 **fluorouracil** 400 mg/m^2 IV bolus then 2400 mg/m^2 IV, D1	13 x 2-week cycles	£30,979
Cetuximab + FOLFOX-4	**cetuximab** 400 mg/m^2 IV for first dose, then 250 mg/m^2 thereafter, D1 and D8 **oxaliplatin** 85 mg/m^2 IV, D1 **folinic acid** 200 mg/m^2 IV, D1 and D2 **fluorouracil** 400 mg/m^2 IV bolus then 600 mg/m^2 IV, D1 and D2	13 x 2-week cycles	£31,692
FOLFIRI	**Irinotecan** 180 mg/m² infusion D1 **folinic acid** 400 mg/m^2 IV infusion D1, **fluorouracil** 400 mg/m^2 IV bolus, then 2400 mg/m^2 IV infusion D1	13 x 2-week cycles	£9,180
FOLFOX-4	**oxaliplatin** 85 mg/m^2 IV infusion D1 **folinic acid** 200 mg/m^2 IV infusion D1 and D2 **fluorouracil** 400 mg/m^2 IV bolus, 600 mg/m^2 IV infusion D1 and D2	13 x 2-week cycles	£9,882
CAPOX	**oxaliplatin** 130 mg/m^2 IV D1 **capecitabine** 1000mg/m^2 orally twice daily, D1 to D14	16 x 3-week cycles	£14,620

See all relevant SPCs for full licensed indications and dosing details[2].
Costs are based on BNF list prices as of July 2015[28]. Cetuximab is available to NHS Wales at a confidential discount on its list price via a WPAS (not included in this table).
Costs of administration and pre-medications are not included.
This table does not imply therapeutic equivalence of the drug regimens or doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, cetuximab (Erbitux®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that cetuximab (Erbitux®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months[1]:

- FIRE-3 (AIO CRC 0306): a randomised trial investigating the efficacy of FOLFIRI in combination with cetuximab versus bevacizumab in the first-line treatment of colorectal cancer[27,29].
- Cancer and Leukemia Group B (CALGB/SWOG C80405) [NCT00265850]: A randomised, open-label, multicentre, phase III trial comparing cetuximab and bevacizumab, in combination with either FOLFOX or FOLFIRI in the first-line treatment of patients with KRAS wild-type untreated mCRC[30].

6.3 AWMSG review
This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search
Date of evidence search: 26 September 2014
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines
The company submission indicates that cetuximab should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[18], as addition of cetuximab to chemotherapy increased median OS by up to 8.2 months, and increased PFS by up to 6.2 months, which the company considers to represent a step change in the treatment of patients with mCRC[1].

The AWMSG criteria for appraising life-extending, end-of-life medicines, and a discussion of the extent to which cetuximab may meet these criteria, are provided in Table 7.

Table 7. Evidence considered by NMG/AWMSG.

AWMSG Criteria for application of the EoL policy (all must apply)[18]	Cetuximab considerations
The most plausible ICER estimate exceeds £30,000 per QALY	It is plausible that the ICER estimates exceed those reported in the base case and so would exceed £30,000 per QALY. PSA helps to confirm this (the probabilities of the ICER estimates falling below £30,000 per QALY is less than 50%) (Section 4).
The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).	The CRYSTAL trial reported median OS in the FOLFIRI alone arm to be 20.2 months. The OPUS trial reported median OS in the FOLFOX-4 alone arm to be 17.8 months[1]. Median OS would therefore seem likely to be less than 24 months based on treatment with FOLFOX-4 or FOLFIRI (Section 3).
There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival	Post hoc subgroup analysis of CRYSTAL trial estimated a statistically significant gain in median OS of 8.2 months with addition of cetuximab to FOLFIRI. The OPUS trial reported a non statistically significant gain of 2.0 months with addition of cetuximab to FOLFOX-4; however, OPUS trial had relatively few RAS wild-type patients providing data (Section 3).
AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small	NICE assumes a "small" population is equivalent to 7,000 patients in England. This would equate to around 406 patients in Wales. The company estimates 322 patients would have met the colorectal cancer indication in 2011. However, using WCISU data[6] and the company's assumptions on the proportion of patients with RAS wild-type mCRC, 515 patients could have potentially met the colorectal cancer indication in 2012 (Section 5). Cetuximab is also licensed for squamous cell carcinoma of the head and neck. In 2011, there were 504 people with head and neck cancer diagnosed within the previous year[31], of which 90% may be squamous cell carcinoma[32]. The cumulative population of each licensed indication would therefore plausibly exceed 406 patients in Wales.
ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); OS: overall survival; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years	

Should NMG/AWMSG conclude that cetuximab should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[18] NMG/AWMSG will need to consider:

- The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age.
- The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the medicine to fall within the current threshold range.

In addition, NMG/AWMSG will need to be satisfied that:

- The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of

trials in which cross-over has occurred and been accounted for in the effectiveness review) and;

- The assumptions used in the economic modelling are plausible, objective and robust.

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