All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA242)

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Final Appraisal Report

Cetuximab (Erbitux®▼) for third-line treatment of patients with KRAS wild-type metastatic colorectal cancer

Merck Serono Ltd

Advice No: 0910

Recommendation of AWMSG

Cetuximab (Erbitux®▼) is not recommended for use within NHS Wales for third-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing, Kirsten Rat Sarcoma (KRAS) wild-type metastatic colorectal cancer.

The case for cost effectiveness had not been proven for the use of cetuximab as either monotherapy or as combination therapy.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 23rd June 2010

The recommendation of AWMSG is:

Cetuximab (Erbitux®▼) is not recommended for use within NHS Wales for third-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing, Kirsten Rat Sarcoma (KRAS) wild-type metastatic colorectal cancer.

The case for cost effectiveness had not been proven for the use of cetuximab as either monotherapy or as combination therapy.

Additional note:

People who are currently being treated with cetuximab (Erbitux®▼) for the indication stated above should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Cetuximab (Erbitux®▼) is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, Kirsten Rat Sarcoma (KRAS) wild-type metastatic colorectal cancer (mCRC)

- in combination with chemotherapy
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Cetuximab (Erbitux®▼) is also indicated for the treatment of patients with squamous cell cancer of the head and neck; details of which can be found in the summary of product characteristics (SPC)[1].

As requested by the Steering Committee of the All Wales Medicines Strategy Group (AWMSG), the company have restricted their submission to the use of cetuximab either in combination with chemotherapy or as monotherapy in patients with the KRAS wild-type gene who have failed two previous chemotherapeutic regimes for mCRC[2].

2.2 Dosing

It is recommended that the detection of KRAS mutational status be performed by an experienced laboratory using a validated test method[1]. The company highlight in their submission that routine KRAS testing is available at the All Wales Molecular Genetics Laboratory, Cardiff[2].

Cetuximab is administered as a once weekly intravenous infusion; given in combination with an antihistamine and/or corticosteroids. The initial dose of cetuximab is 400mg/m^2 body surface area (BSA), followed by subsequent weekly doses of 250mg/m^2 BSA. It is recommended that the weekly doses are continued until there is progression of the underlying disease. Close monitoring is required during the infusion and for at least one hour after the end of the infusion. Availability of resuscitation equipment must be ensured[1].

For the dosage or recommended dose modifications of concomitantly used chemotherapeutic agents, please refer to the product information for these specific agents. They must not be administered earlier than one hour after the end of the cetuximab infusion[1].

2.3 Market authorisation date

Approval of the revised indication relating to KRAS wild-type mCRC was granted on 17th July 2008[3].

2.4 UK Launch date

24th September 2008[4].

3.0 DECISION CONTEXT

3.1 Background

Colorectal cancer is the third most common cancer in the UK, with approximately 30,000 new cases registered in England and Wales in 2002 and the incidence increasing with age[5]. The estimated proportion of patients presenting with mCRC ranges from 20% to 55% of all new cases, with a five year survival rate of 12%[5].

The management of mCRC is mainly palliative and involves a combination of palliative surgery, symptom control, chemotherapy and radiotherapy. EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis[1]. Cetuximab blocks binding of endogenous EGFR ligands thus inhibiting receptor function. It further induces EGFR internalisation, which can lead to down-regulation. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells[1].

The licence for cetuximab covers EGFR-expressing, KRAS wild-type mCRC. The efficacy and safety of cetuximab have only been documented in patients with tumours where EGFR was detected[1] but the importance of the level of EFGR expression is currently unknown[3]. The KRAS gene can be expressed as a non-mutated version which is called wild-type or as a mutant version. Mutations in the KRAS gene confer resistance to EGFR inhibition and the KRAS status of patients may therefore be predictive for a response or non-response[2]. Extensive data demonstrate that the use of cetuximab should be restricted to patients with tumours not harbouring activating KRAS mutations[3]. In mCRC, the incidence of KRAS mutations is in the range of 30 to 50% and patients with KRAS wild-type mCRC have a significantly higher chance of benefiting from treatment with cetuximab or a combination of cetuximab and chemotherapy[1].

After applying a rate of 54% for KRAS wild-type tumours (see section 6.0), and 80% for EGFR-expressing disease, there are approximately 263 patients in Wales of which company-sought expert opinion believe only 50% would be suitable for third-line cetuximab therapy, i.e. 132 patients[2]. The company believe that the use of cetuximab in this patient population meets the end of life criteria set by the National Institute for Health and Clinical Excellence (NICE)[6]. This is based on the fact that both as monotherapy and in combination with chemotherapy, cetuximab may increase overall survival (OS) by more than three months compared to the most relevant comparator (best supportive care [BSC]) in a population whose survival is no more than two years. In addition, the cumulative population for which cetuximab can be prescribed is considered by the company to be small[2].

3.2 Comparators

Company-provided market research data in ≥ third-line treatment settings lists the frequency of use of irinotecan and 5-fluorouracil agents as both approximately 46%, followed by capecitabine at 36%, oxaliplatin at 23%, folinic acid at 9% and other agents at 18% (including combination therapies)[2].

There are very few treatment options in the third-line setting and only a small number of patients survive long enough and are fit enough to receive cytotoxic treatment in this setting. Normal practice appears to be mixed, with many patients likely to just receive palliation[2]. BSC is therefore considered the most relevant comparator in this setting.

3.3 Guidance and related advice

- NICE issued a technology appraisal of bevacizumab and cetuximab for the treatment of mCRC in January 2007[5]. Cetuximab in combination with irinotecan is not recommended for second-line or subsequent treatment of mCRC after failure of an irinotecan-containing chemotherapy regimen.
- In June 2006, the AWMSG recommended cetuximab for use in combination with irinotecan in NHS Wales with specific restrictions applied[7]. This advice was subsequently superseded by NICE.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main evidence focuses on two relevant retrospective KRAS analyses of participants in previous trials that involved the use of cetuximab either as monotherapy or as combination therapy in mCRC compared to BSC. In the first analysis (n=113) where most (86.8%) patients had received at least two previous lines of chemotherapy, median progression free survival (PFS) and OS were only significantly different between the wild-type versus mutant KRAS status in the combination therapy group and not in the monotherapy group. The majority of patients (81.9%) in this analysis, however, had received cetuximab (250mg/m^2) as combination therapy. Retrospective subgroup analysis (n=394) from the second study (CO17 study) did demonstrate that KRAS wild-type mCRC patients had a significant increase in OS and PFS following treatment with cetuximab monotherapy after two previous lines of chemotherapy had failed. The mutation status of the KRAS gene was shown to have no influence on survival amongst patients treated with BSC alone. Severe infusion-related reactions may commonly occur. However the Committee for Medicinal Products for Human Use (CHMP) considered overall that the toxicity profile of cetuximab, as discussed in the context of the licence extension, is in line with the already known adverse reaction profile for cetuximab.

4.2 Review of the evidence on cost-effectiveness

The company has conducted cost utility analyses of cetuximab alone, and in combination with irinotecan, both compared against BSC, as third-line treatment for mCRC.

In the base case analysis, using the company-reported current NHS cost (which remains confidential), the incremental cost per quality-adjusted life year (QALY) gained for cetuximab in combination with irinotecan versus BSC is £41,364 and for cetuximab monotherapy versus BSC is £53,808. There are, however, a number of limitations to the analyses. The key efficacy parameters in the model are OS and PFS, which are derived from retrospective analyses conducted in sub-groups of trial populations. In the absence of direct comparative efficacy data for combination therapy versus BSC, these are derived from indirect comparisons, which have inherent limitations. Although BSC is the common comparator, with efficacy data derived from the same sources, the cetuximab monotherapy and combination therapy models differ in their approaches to extrapolation of survival data in the longer term and the inclusion of adverse events, with the effect that overall costs and outcomes for BSC are different between the two models.

The company has provided additional, confidential analyses using a reduced cetuximab cost in line with the NICE technology appraisal of cetuximab as first-line treatment.

4.3 Limitations of the evidence

- A limitation of the clinical evidence is that all the analyses are retrospective and not planned (*a priori)*.
- The key efficacy parameters in the economic model are derived from these retrospective analyses conducted in sub-groups of trial populations. There are no direct comparative data versus the BSC comparator in the combination therapy model, and indirect comparisons have been conducted, which have inherent limitations.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

The company submission includes evidence for the use of cetuximab in combination with irinotecan (the Bowel Oncology with Cetuximab Antibody [BOND] trial) on which the original licence granted for cetuximab following failure of irinotecan-containing therapy was based[8-10]. The phase II trial[11] also formed the main body of evidence for a previous AWMSG recommendation for use of this technology in a different setting[8]. In addition the company highlight the Monoclonal Antibody Erbitux®▼ in a European Pre-Licence Study (MABEL); a phase II trial designed to provide additional safety and efficacy information on the combination of cetuximab plus irinotecan in patients who had progressed on an irinotecan-based regimen and to confirm the findings of the BOND study in a wider standard community practice setting[2]. The company have also submitted data for the use of cetuximab as monotherapy (CO17 study)[11].

KRAS status, however, was not a prerequisite to inclusion in these studies (no conclusive evidence for potentially predictive biomarkers was available at the time) and the global population of these trials can not be used to evaluate the benefits specifically associated with cetuximab in previously treated KRAS wild-type mCRC patients[2]. The company recognised the need therefore to gather additional evidence by undertaking a systematic review and identifying supportive studies focussing on relevant retrospective KRAS analyses of participants in previous trials that involved the use of cetuximab either as monotherapy or as combination therapy in mCRC. However, the company confirmed that it was not possible to use the output of the systematic review within an indirect comparison[2].

Although a number of supportive studies focussing on relevant retrospective KRAS analysis were identified (see Table 1B, Appendix 1), it was not possible to pool clinical outcomes because of differences in study designs. Two out of ten studies identified reported both PFS and OS[12,13]. Both studies have shown objective response (OR) (i.e. complete response plus partial response [CR+PR]) to cetuximab to be excluded in KRAS-mutated CRC and notably, to have shown an increase in OS for KRAS wild-type patients. The larger of the two studies has been highlighted by the company in their submission for the comparison of cetuximab plus irinotecan to BSC and is discussed below[12] along with a retrospective sub-group analysis of the CO17 study according to KRAS status for the cetuximab monotherapy comparison to BSC [11,14]. Both studies are used in the economic analysis (see section 7.1.1).

5.1 Clinical evidence

5.1.1 De Roock and colleagues

This review was a retrospective analysis of four clinical studies (BOND, EVEREST, SALVAGE and BABEL)[12]. A total of 113 irinotecan-refractory mCRC EGFR-expressing patients were included. Most (86.8%) of the patients had received two or more previous lines of chemotherapy, and the majority (81.9%) of patients had received combination therapy (i.e. cetuximab 250mg/m^2 plus irinotecan)[12].

KRAS mutations were detected in 46 of 113 (40.7%) tumours. OR rate was 27 of 66 (41%) in wild-type KRAS patients compared to a zero OR in 42 patients with KRAS mutation. The impact of KRAS mutation state on OR rate was found only to be significantly different in the combination group ($p<0.001$). An OR was observed exclusively in the KRAS wild-type group of patients. Median PFS and OS were only significantly different between the wild-type versus mutant KRAS status in the combination therapy group and not in the monotherapy group[12]. See Appendix 1, Table 1A, for details of the results.

5.1.2 CO17 study

The CO17 trial randomised 572 patients to receive cetuximab plus BSC (n=287) or BSC alone (n=285)[11]. A subgroup analysis on their KRAS status to examine the efficacy of cetuximab in relation to KRAS genetic subgroups was retrospectively carried out[14]. The results of this sub-group analysis (n=394) demonstrated that KRAS wild-type mCRC patients had a significant increase in OS and PFS following treatment with cetuximab monotherapy after two previous lines of chemotherapy had failed. The mutation status of the KRAS gene had no influence on survival amongst patients treated with BSC alone[14]. See Appendix 1, Table 1A, for details of the results.

The Health Related Quality of Life (HRQL) amongst patients with wild-type KRAS tumours was also assessed[14]. Those in the cetuximab group showed improvement in global health status at eight weeks, not seen in the BSC alone group (mean change in score 3.2 versus -7.7 points, difference: 10.9; 95% confidence interval [CI]: 4.2 to 17.6; p=0.002). Patients in the cetuximab group also had less deterioration at 16 weeks (mean change in score -0.2 versus -18.1 points; difference, 17.9; 95% CI: 7.6 to 28.2; p<0.001)[14]. There was no significant difference shown in global health status for patients with mutated KRAS[14].

5.2 Safety

Severe infusion-related reactions may commonly occur; in rare cases with a fatal outcome. They usually develop during or within one hour of the initial cetuximab infusion, but may occur after several hours or with subsequent infusions. Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature. In rare cases, angina pectoris, myocardial infarction (MI) or cardiac arrest, have been observed[1].

Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash. Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed (see SPC for further details)[1].

In combination with platinum-based chemotherapy, the frequency of severe leucopenia or severe neutropenia may be increased, and in combination with infusional 5-fluorouracil, the frequency of cardiac ischaemia (including MI and congestive heart failure) were increased compared to that with infusional 5-fluorouracil alone[1].

CHMP considered overall however that the toxicity profile of cetuximab, as discussed in the context of the licence extension, is in line with the already known adverse reaction profile, including skin-related reactions, pyrexia, stomatitis, headache, conjunctivitis, and hypomagnesaemia[3]. In addition, the add-on toxicity was considered manageable and acceptable in patients with mCRC assumed to benefit from standard chemotherapy cetuximab as add-on therapy[3].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The licence extension for KRAS wild-type mCRC covers both previously treated and previously untreated patients and was granted on the basis of a retrospective KRAS subgroup analysis in the pivotal studies, OPUS (Oxaliplatin and Cetuximab in first-line treatment of mCRC) and CRYSTAL (Cetuximab Combined with Irinotecan in first-line therapy for mCRC)[3]. In response to the request made by the AWMSG steering committee, the company have restricted their submission to the use of cetuximab either in combination with chemotherapy or as monotherapy in patients with the KRAS wild-type gene who have failed two previous chemotherapeutic regimes for mCRC (i.e. third-line setting)[2].
- A limitation of the clinical evidence is that all the analyses are retrospective and not planned (*a priori)*. Retrospective analysis of patients was necessary because no conclusive evidence for potentially predictive biomarkers was available at the time of the original trials.
- Clinical outcomes such as OS, response and toxicity are important, but also alternative outcomes such a PFS and quality of life are also recognised as important markers[3]. Only two of the retrospective studies assessed both PFS and OS[12,13], and PFS was assessed by the investigator. This is not ideal for open label studies, but acceptable here as survival was also a primary endpoint.
- Not all of the other supportive studies provided relevant outcomes or where median PFS or median OS were available, previous chemotherapy lines were not always reported (see Appendix 1, Table 1B,}. Limited data was therefore available in terms of the use of cetuximab either in combination with chemotherapy or as monotherapy specifically in patients with the KRAS wild-type gene who have failed two previous chemotherapeutic regimes for mCRC.
- Clinical trial data suggests the split between KRAS wild-type and KRAS mutant patients is approximately 60:40% respectively; however a figure quoted by the company from KRAS testing laboratories for Welsh patients suggests that from actual experience in testing, this figure is more likely to be 54% for KRAS wild-type patients[2].
- The company highlight in their submission that all patients must be tested for KRAS status and only KRAS wild-type patients are eligible for cetuximab. In addition, patients must be able to tolerate further lines of chemotherapy and be able to tolerate the skin rash commonly associated with cetuximab therapy.
- In Study CO17 most patients (76.7%) were relatively fit (i.e. they had an Eastern Cooperative Oncology Group (ECOG) performance score between 0 and 1)[11].

7.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

7.1 Cost-effectiveness evidence

7.1.1 Context

The company has conducted cost utility analyses of cetuximab alone, and in combination with irinotecan, both compared against BSC as third-line treatment for mCRC[2]. This represents a sub-group of the licensed indication[14]. Direct comparative data from a retrospective analysis of patients with KRAS wild-type status that form a sub-group of study CO17[14] are employed for the analysis of cetuximab monotherapy versus BSC. For the analysis of cetuximab in combination with irinotecan versus BSC, an indirect comparison has been undertaken using survival data from study CO17[14] and from a retrospective analysis of four studies of cetuximab in combination with chemotherapy in irinotecan-refractory patients[12]. Further details of the modelling approach are described in Appendix 2.

The analysis is conducted from the perspective of NHS Wales using a lifetime time horizon. In the base case analysis, the cost assumed for cetuximab is the current NHS cost of cetuximab, which is lower than the current UK list price. Scenario analyses have been conducted to explore cetuximab acquisition cost, including a 16% rebate on the current NHS cost, in line with the terms of use of cetuximab as first-line therapy set out in NICE Technology Appraisal No. 176, August 2009[15]. The company has also provided analyses to explore the QALY weighting required to bring the incremental cost effectiveness ratio (ICER) to within £20,000 and £30,000 per QALY gained, should cetuximab be judged to meet the criteria for end of life considerations.

7.1.2 Results

In the base case analysis, using the company-reported current NHS cost (which remains confidential), the incremental cost per QALY gained for cetuximab in combination with irinotecan versus BSC is £41,364 (based on additional costs of £31,054 and a gain of 0.751 QALYs). For cetuximab monotherapy versus BSC, the incremental cost per QALY gained is reported in the company submission as £53,808 (based on additional costs of £14,778 and a gain of 0.275 QALYs)[1] (see Table 1).

Table 1. Base case analyses using current NHS price for cetuximab (i.e. not list price) as reported in the company submission[2]

Combination model		
	Cetuximab + irinotecan	**BSC**
Total costs	£37,639	£6,585
Total LYG	1.430	0.547
Total QALYs	1.142	0.391
ICER (£/QALY gained)	**£41,364**	
Monotherapy model		
	Cetuximab + BSC	**BSC**
Total costs	£18,266	£3,489
Total QALYs	0.686	0.411
ICER (£/QALY gained)	**£53,808**	

BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life year gained

Scenario analyses: At the company-reported UK list price, the incremental cost per QALY gained for combination therapy is £49,217, and for monotherapy is £63,001[2] (see Table 2). A scheme highlighted by the company in their submission which would reduce the NHS acquisition cost was also considered, however these figures remain confidential. The analyses of end of life QALY weightings required to bring the ICERs within £20,000 and £30,000 per QALY gained are also presented in Table 2. For the base case model, each QALY gained with combination therapy must be valued 2.07 times greater than a 'typical' QALY for the ICER to fall within £20,000 per QALY gained, and 1.38 times greater to fall within £30,000 per QALY gained.

Table 2. Key scenario analyses and probabilistic sensitivity analyses (PSA)[2]

	Combination therapy (ICERs £/QALY gained)	Monotherapy (ICERs £/QALY gained)
Cetuximab cost scenarios		
UK list price (£1.781/mg)*	£49,217	£65,066
End of life criteria – QALY weighting to achieve cost-effectiveness thresholds		
Base case		
£20,000/QALY	2.07	2.69
£30,000/QALY	1.38	1.79
PSA – cost-effectiveness probabilities at thresholds		
Base case		
£20,000/QALY	12.5%	0%
£30,000/QALY	28.6%	0.2%
UK list price (£1.781/mg)*		
£20,000/QALY	7.3%	0%
£30,000/QALY	19.7%	0.1%

ICER: Incremental cost effectiveness ratio; PSA: Probabilistic sensitivity analyses; QALY: Quality-adjusted life year. *Company-reported UK list price, but note this is greater than the current list price in BNF No. 58[16].

Sensitivity analyses: Univariate sensitivity analyses indicate that the combination therapy model is most sensitive to the assumed hazard ratio (HR) for OS and PFS, derived from the indirect comparison. When the HR for OS in the base case analysis was explored within the range of its 95% CI, the ICER ranged from £19,726 to £117,409 per QALY gained. For PFS, the ICER ranged from £24,812 to £65,692 per QALY gained. Results of PSA, which aim to capture the combined uncertainty in several parameter value estimates, are presented in Table 2. The probability of cetuximab combination therapy being cost effective at a threshold of £20,000 per QALY gained is less than 15%, and at a threshold of £30,000 per QALY gained is less than 35%, in all cost scenarios that are explored. CIs for the estimated ICERs have not been provided.

7.1.3 WMP Critique

Strengths of the economic evidence:

- The monotherapy model uses patient-level data from a pivotal, direct comparative trial.
- Numerous scenario and sensitivity analyses have been conducted to address relevant areas of uncertainty in the modelling methods and the decision problem.

Limitations of the economic evidence:

- There are no direct comparative data for combination therapy versus BSC. A statistical indirect comparison has been performed, which has inherent limitations that are compounded by the fact that the data are derived from retrospective analyses conducted in sub-groups of the trial populations. The combination therapy model is very sensitive to the assumed OS and PFS with combination therapy.
- BSC is the comparator in both models, but is accounted for differently within the models. The company has included the costs of adverse events associated with BSC in the combination therapy model, but not in the monotherapy model, on the basis that the comparisons made within each model are qualitatively different. It is unclear how appropriate this assumption is and whether or not this introduces bias in favour of cetuximab plus irinotecan in the combination model or in favour of BSC in the monotherapy model. It should also be noted that different approaches have been used for extrapolating survival in the combination therapy and monotherapy models, which compounds the uncertainty and potential bias.
- In the absence of relevant data, adverse event rates and utility values for cetuximab combination therapy are assumed to be the same as for cetuximab monotherapy.

7.2 Review of published evidence on cost-effectiveness

Standard WMP searches have identified a published cost utility analysis of cetuximab as monotherapy versus BSC in the Canadian health setting, that was unfunded, and based on study CO17[17]. For patients with wild-type KRAS tumours and using data collected as part of the trial, the calculated number of QALYs with cetuximab monotherapy was 0.51 over an 18-19 months time horizon (compared with 0.686 over four years in the company model), and with BSC was 0.33 (compared with 0.411 in the company model). The incremental QALY gain was therefore 0.18 over the course of the trial, compared with 0.275 over four years in the company submission. The incremental cost with cetuximab was $33,617, resulting in an incremental cost-utility ratio of $186,761 per QALY gained (95% CI = $130,326 to $334,940 per QALY gained). In a sensitivity analysis, cetuximab cost and patient survival were the only variables that influenced cost-effectiveness.

As this analysis was conducted in a Canadian health setting, the interpretation of the ICER is limited. It is based on the same data set as is used in the monotherapy model in the company submission, and it is apparent that the mean gains in QALYs are considerably lower in this published analysis than are estimated in the company submission[2], but this may be due to differences in the modelling approaches and time horizons of analysis.

8.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

8.1 Budget impact evidence

8.1.1 Context

The budget impact analysis relates to the use of cetuximab, either alone or in combination with irinotecan, in the third-line treatment of colorectal cancer[2]. As cetuximab treatment is given in addition to BSC, the budget impact relates only to the costs of the addition of cetuximab (+/- irinotecan) to BSC.

8.1.2 Methods

The incidence of colorectal cancer has been derived from historical Welsh Cancer Surveillance data, which has been extrapolated over the five years 2010 to 2014[2]. Due to the limited life expectancy of patients, it is assumed that prevalence is equal to incidence[2]. Reportedly based on company-sought Welsh expert opinion and trial populations, it is estimated that that there will be 135 patients eligible for third-line treatment with cetuximab in 2010, rising to 149 in 2014. Uptake of cetuximab in 2010 is estimated to be 15%, rising to 90% in 2014. Of patients eligible for cetuximab, it is assumed that 80% will receive it in combination with irinotecan and 20% will receive it as monotherapy[2]. Direct costs considered in the analysis are related to drug acquisition and administration (infusion) costs, which are reported to have been derived from the economic models for combination therapy and monotherapy.

8.1.3 Results

Table 3. Company estimates of additional cost from use of cetuximab (+/- irinotecan) in third-line treatment of mCRC[2]

	2010	2011	2012	2013	2014
Eligible patients	135	139	142	145	149
Uptake	15%	50%	65%	80%	90%
Cetuximab treated patients	20	70	92	116	134
Additional cost	**£538,888**	**£1,886,108**	**£2,485,676**	**£3,128,946**	**£3,607,154**

The company has provided additional one-way scenario analyses to explore the impact of a +/-10% change in prevalence; an increase of 10% in the proportions of patients estimated to be offered first, second or third line treatment; and a faster rate of uptake (50% in year 1 rising to 100% in year 5. Results are as would be expected.

8.1.4 WMP Critique

The costs assumed in the budget impact analysis are derived from the economic model. The base case economic models use the company-reported NHS cetuximab acquisition cost that is lower than the current UK list price, and the costs of infusion assumed in the models appear subject to some uncertainty. A range of assumptions are employed, from modelling of incidence based on historical data through to estimated eligibility rates and uptake, which have not been further explored in the budget impact analysis.

8.2 Comparative unit costs

It is not possible to derive comparative unit costs for the use of cetuximab in the third-line treatment of mCRC, as BSC is considered the appropriate comparator and may be composed of a range of treatments individually tailored to patients.

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

- Cetuximab (Erbitux®▼) must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring during the infusion is also required[1]. Cetuximab (Erbitux®▼) is therefore not considered suitable for shared care.

9.2 Patient Organisation Information

A patient organisation submission by was not received.

9.3 Medical expert/Clinical expert summary

A summary of medical/clinical expert views was provided.

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Appendix 1. Additional Clinical Information

Table 1A. Most relevant studies which include analysis of KRAS wild-type patients

Ref	Study type	No. patients	Inclusion/ exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes
2, 12	Retrospective analysis of four clinical studies: BABEL, BOND, EVEREST and SAVAGE	Total no. of patients n=113		**For KRAS wild-type patients (n=67):** Mean age (SD): 58.8 (11.5) Male: 44 (65.7%) Female: 23 (34.3%) No. of previous lines of chemotherapy ≥2: 2 (n=30; 44.8%) 3 (n=23; 34.3%) 4 (n=4; 6.0%) 5 (n=3; 4.5%)	**For KRAS wild-type patients (n=67):** Cetuximab monotherapy: n=18 (26.9%) Cetuximab 250mg/m^2 +irinotecan: n=37 (75.5%) Cetuximab 300mg/m^2 +irinotecan: n=1 (2.0%) Cetuximab 350mg/m^2 +irinotecan: n=4 (8.2%) Cetuximab 500mg/m^2 +irinotecan: n= 7 (14.3%)	**(Wild-type KRAS versus mutant type)** **Survival analysis results** **Median PFS, wks (95% CI):** Combination therapy: 34wks (28.5 to 40.0) vs 12wks (5.4 to 18.7); p=0.016 Monotherapy: 12wks (4.2 to 20.0) vs 12wks (7.0 to 17.0); NS **Median OS, wks (95% CI):** Combination therapy: 44.7wks (28.4 to 61.0) vs 27.3wks (9.5 to 45.0); p=0.003 Monotherapy: 27wks (8.9 to 45.1) vs 25.3wks (0.0 to 70.0); NS
2, 11,14	Open-label study and retrospective analysis	Randomised, open-label study CO17 n=572 Retrospective analysis of study CO17 n=394; 68.9%	**Inclusion:** Treatment with a fluoropyridimine with no response to treatment; ECOG performance status 0 to 2; adequate bone marrow, kidney and liver function; no serious concurrent illness; **Exclusion:** Treatment with agent that targets EGFR pathway or a murine monoclonal antibody	Patients from the original study were stratified according to centre and ECOG performance status (i.e. 0 versus 1 or 2)	Patients were Randomised 1:1 ratio to either cetuximab plus BSC or BSC alone IV cetuximab 400mg /m^2 BSA was administered initially followed by weekly IV cetuximab 250mg/m^2 BSA until death	**(Cetuximab+BSC versus BSC)** **Results for all patients (n=572):** **Median OS:** 6.1mths (n=287) vs 4.6mths (n=285); HR 0.77; 95% CI: 0.64 to 0.92); p=0.005 **Median PFS:** Not reported; HR 0.68; 95% CI: 0.57 to 0.80; p<0.001 **Results for KRAS mutant patients (n=164):** **Median OS:** 4.5mths (n=81) vs 4.6mths (n=83); HR 0.98; 95% CI: 0.70 to 1.37); NS **Median PFS:** 1.8mths (n=81) vs 1.8mths (n=83); HR 0.86; 95%CI: 0.57-0.80; NS **Results for patients with wild-type KRAS (n=230):** **Median OS:** 9.5mths (n=117) vs 4.8mths (n=113); HR 0.55; 95%CI: 0.41- 0.74; p<0.001. **Median PFS:** 3.7mths (n=117) vs 1.9mths (n=113); HR 0.40; 95%CI: 0.30-0.54; p<0.001.

BSC: best supportive care; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; KRAS: Kirsten Rat Sarcoma; OS: overall survival, NS: not significant; PFS: progression free survival; SD: standard deviation

Table 1B. Description of additional supportive studies

Ref	Number of patients	No. of previous chemotherapy lines	KRAS status	Cetuximab mono Or combination therapy	Relevant outcomes, PFS or OS
18	48 EGFR expressing mCRC patients who previously enrolled into trials of panitumumab or cetuximab. 12 patients received cetuximab monotherapy, 25 received panitumumab monotherapy and 11 received cetuximab plus irinotecan based chemotherapy	1/11 patients that received cetuximab plus irinotecan as 2nd line treatment and 4/11 patients received it as 3rd line treatment	KRAS mutations were detected in 16/48 (33.3%) patients 32/48 patients expressed wild-type KRAS	Cetuximab was administered either as monotherapy or combination therapy	Not evaluated
19	85 chemorefractory mCRC patients.	Two: 34/85 (40%) of patients ≥ three: 30/85 (35.3%) of patients 90.6% patients have tried a cetuximab+irinotecan regimen.	No KRAS analysis were performed in this trial	Cetuximab was administered either as monotherapy or combination therapy	Not reported
20	59 chemorefractory patients	Patients have received at least one CT regimen.	KRAS wild-type, n=43 KRAS mutant, n=16	Cetuximab +/- irinotecan or oxaliplatin	Not evaluated
21	Tumour blocks from 85 patients cetuximab were analysed for EGFR and KRAS	Not reported	KRAS wild-type, n=49 KRAS mutant, n=32	Cetuximab monotherapy	OS was 10.8 months in the wild-type arm versus 8.3 months in the mutant arm (p=0.2)
22	110 patients with mCRC	38/110 patients have tried two chemotherapy lines	KRAS wild-type, n=50 KRAS mutant, n=30	Cetuximab monotherapy	mPFS was 61 days for the wild-type arm vs 59 days for the mutant arm HR = 1.4; 95% CI, 0.87 to 2.6; median, p=0.14
23	76 EGFR expressing mCRC	Not reported	KRAS wild-type, n=49 KRAS mutant, n=27	Cetuximab or with cetuximab + irinotecan based regimen.	mPFS was 32 weeks for the wild-type arm versus 8.6 weeks for the mutant arm $p<5.10^{-6}$
13,24	89 patients with advanced mCRC after treatment failure with irinotecan-based chemotherapy	Cetuximab administered second-line, third-line, fourth-line, or fifth-line therapy or more in 8, 37, 29, and 15 patients, respectively			mPFS was 31.4 weeks (95% CI: 19.4 to 36) for the wild-type arm versus 10.1 weeks (95% CI: 8 to 16) for the mutant arm (p=0.0001). mOS was14.3 months (95% CI: 9.4 to 20) for the wild type arm versus 10.1 months (95% CI: 5.1 to 13) for the mutant arm (p=0.026).
25	31 patients with mCRC	8/31 patients have received 2 previous chemotherapy lines	21 patients expressed KRAS wild-type	Cetuximab mono- and combination therapy	OS and PFS not evaluated in this trial

EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma; mCRC: metastatic colorectal cancer; OS: overall survival; PFS: progression free survival

Appendix 2. Additional Health Economic Information

Table 2A. Health economic model detail[2]

Base Case Model		Appropriate?
Comparator(s)	i) Cetuximab (400mg/m^2 week 1 the 250mg/m^2 weekly) + irinotecan (180mg/m^2 every 2 weeks) versus BSC ii) Cetuximab (400mg/m^2 week 1 the 250mg/m^2 weekly) + BSC versus BSC	Yes for the population considered in the analyses.
Population	Patients with mCRC who have failed two previous lines of therapy, and have ECOG performance status 0 or 1. Patients assumed to have body surface areas of 1.75m^2.	Represents a sub-group of the licensed population. The licensed indication does not specify its use in combination with chemotherapy only in those who have failed previous therapy. Patients are assumed to have good performance status and be suitable candidates for cetuximab alone, or in combination with irinotecan.
Model type and description	Model represents three health states: progression-free; progressive disease; and death. Monte Carlo simulation used to propagate uncertainty of input variables. Probabilistic sensitivity analyses based on 2,000 iterations.	The approach taken appears adequate for modelling the clinical pathway of the population considered in the analyses. Appropriate distributions appear to have been used for probabilistic sensitivity analysis. However, the company-reported model outputs for the monotherapy model appear to be based on life years gained, rather than QALYs, as discussed in section 6.1.3.
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time horizon	Model runs for 200 one-week cycles, which is approximately 4 years	The company considers this to represent a lifetime analysis, which would be appropriate for this population. The OS curves for combination therapy suggest that around 95% of patients are dead at this time point.
Discount rate	Costs and outcomes discounted at 3.5% per annum, rates of 0% and 6% explored in sensitivity analysis	Yes
Efficacy	PFS and OS are the main outcome measures used in the model. For cetuximab monotherapy, the probabilities of progression and death relative to BSC are derived from post hoc analyses of study CO17[2]. For combination therapy, an indirect comparison of survival data from post hoc analyses of study CO17 of cetuximab monotherapy versus BSC[2] and from a retrospective analysis of four studies of cetuximab in combination with chemotherapy in irinotecan-refractory patients[3]. The OS and PFS curves obtained from the BSC arm of study CO17 have been extrapolated using Weibull and/or log-logistic functions. For combination therapy, these curves have been adjusted using the HRs for PFS and OS obtained from the indirect comparison.	Appropriate to use these outcome measures in the model. Survival data for cetuximab plus irinotecan versus cetuximab monotherapy are derived from a retrospective analysis of four trials. It is unclear whether these are the only trials that might have informed the analysis. These trials were not designed to compare the effects of treatment by KRAS status nor were they designed to compare combination therapy versus cetuximab monotherapy in patients with KRAS wild type. Pooled data in the retrospective analysis are based on small numbers of patients (49 combination therapy and 18 cetuximab monotherapy). These data have been used in an indirect comparison with data from a post hoc analysis of study CO17, which are based on <40% of the original CO17 trial population, to provide an estimate of survival with combination therapy relative to BSC. The actual HRs for OS and PFS for combination therapy versus cetuximab monotherapy, and for PFS for BSC versus cetuximab monotherapy have not been confirmed from the cited sources. Retrospective, post hoc analyses should be interpreted with caution, and indirect comparisons have inherent limitations. Collectively, there would appear to be several sources of uncertainty in the key parameters driving the model.

Table 2A. Continued

Adverse effects	Included in the model as non-serious events requiring outpatient visit, serious events requiring inpatient stay or serious events requiring outpatient visit, reportedly based on patient level data from CO17; reported to have been classified by severity and body system and mapped to suitable NHS reference costs to produce an average cost per event. No further details are provided of rates of events, etc.	Patient level data from study CO17 have been used to model adverse events for patients receiving both cetuximab monotherapy and cetuximab plus irinotecan, which would be a potential source of uncertainty.
Utility values	Quality of life was assessed at multiple time points in study CO17 using a generic instrument. This has been used to derive utility values for pre- and post-progression health states.	Appropriate to use trial derived utility data. However, it is not clear that utility values have been derived specifically for the patient population that has been modelled. In addition, utility values for patients receiving cetuximab monotherapy have been assumed for patients receiving cetuximab in combination with irinotecan.
Resource use	Consists of drug acquisition and administration as per the clinical trials, adverse event management, KRAS testing for cetuximab recipients, Specialist and GP visits, and BSC resource use. In addition, an end of life cost, based on 14 days of specialist palliative care is assumed. Patient level data from study CO17 reportedly used for both combination therapy versus BSC and for cetuximab monotherapy vs BSC.	Appropriate to incorporate these items of resource use based on patient level data in the KRAS wild type subset, although not possible to verify these from the sources provided.
Costs	Resource use costed using published sources, including BNF, NHS reference costs. In the base case analysis, the cost assumed for cetuximab (which remains confidential), is stated to be the current cost of cetuximab to NHS Wales. The submission indicates that the list price is £1.781/mg.	The reported sources of costs associated with resource use are appropriate; however, the costs of administration in the cetuximab plus irinotecan combination model are lower than that reported in the submission and used in the cetuximab monotherapy model, and the costs of concomitant chemotherapy pre- and post-progression are lower in the monotherapy model than those reported in the submission and in the combination model. Three cetuximab acquisition cost scenarios have been presented. The base case analyses in both models use a cetuximab cost per mg (which remains confidential), which the company submission states is the current NHS cost of cetuximab. A scenario analysis has been provided using a cost per mg of £1.781, which the company submission implies is the current UK list price based on the current BNF and indicates that this is not currently used in the UK (however, this is greater than the cost in the current BNF, which is equivalent to £1.5902 per mg)[6]. A further scenario analysis is provided in which the cost of cetuximab is 16% lower than what the company claims is the current NHS price (i.e. 16% lower than £1.365 per mg). This is reported in the submission to be in line with the terms of use of cetuximab as first-line therapy set out in NICE technology appraisal No. 176, August 2009[4]. This is operated as a rebate based on 16% of the amount of cetuximab used on a per patient basis[4]. Cetuximab (and irinotecan) are costed on a per mg basis, which implicitly assumes no vial wastage.
Model Provided?	Yes	Yes
Other considerations	End of life considerations	
BNF: British National Formulary; BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; KRAS: Kirsten Rat Sarcoma; OS: Overall survival; PFS: Progression free survival; QALY: quality adjusted life years.		