1. Executive summary

1.1 Drug Particulars

Approved name: cetuximab
Brand name: Erbitux®

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).
The following vial sizes are available:
100mg cetuximab/20ml vial and 500mg cetuximab/100ml vial.

Cetuximab in combination with chemotherapy or as monotherapy is administered using the following regimen: 400 mg cetuximab per m^2 body surface area on day 1. All subsequent weekly doses are 250 mg/m^2 each. Cetuximab treatment is continued until progression of the underlying disease.

List Price:	£178.10/20ml vial; £890.50/100ml vial
Agreed NHS Price:	£136.50/20ml vial; £682.50/100ml vial

Relevant Licensed Indications
Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer.

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

Scope of the NICE submission
Merck Serono will be submitting evidence for the use of cetuximab in combination with chemotherapy or as monotherapy in patients with EGFR-expressing KRAS wild-type metastatic colorectal cancer who have failed at least two previous chemotherapeutic regimens in the metastatic setting. The decision to submit evidence for the use of cetuximab in combination with chemotherapy or as monotherapy in the third and subsequent line is based on clinical need, the strength of the evidence, Expert Opinion and current usage.

1.2 Background and Epidemiology

Colorectal cancer, cancer of the colon and rectum, is one of the most common cancers in the UK. In advanced colorectal cancer, also known as metastatic colorectal cancer the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body.

There are a limited number of technologies licensed for the treatment of the metastatic stage in Europe and in use within the NHS and third line therapy in mCRC is deprived of effective treatment improving patient survival. At this stage of disease the remaining option is best supportive care. A few technologies have recently obtained a licensed indication after first line chemotherapy for the treatment of metastatic colorectal cancer which include cetuximab, bevacizumab and panitumumab.

Cetuximab was first granted a marketing authorisation in 2004 for the treatment of EGFR-expressing, metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy. At this time, there was no conclusive evidence to indicate the role of KRAS status as a predictive biomarker for cetuximab. Issued in January 2007, NICE technology appraisal 118 reviewed the use of cetuximab within its initial licensed indication (NICE TA 118). This multiple technology appraisal includes a part-review of NICE TA 118.

A revised licence for cetuximab has since been granted (July 2008) for the treatment of metastatic colorectal cancer. The revised marketing authorisation for metastatic colorectal cancer states that cetuximab is indicated for the treatment of 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. The licence extension was granted

based on retrospective analyses of CRYSTAL (EMR 62202-013) and OPUS (EMR 62 202-047) in the first line setting and CO.17 (CA225025) in the pre-treated setting.

Effectively, cetuximab offers an important treatment option to patients who have been exposed to the three backbone chemotherapy agents i.e. 5-FU, oxaliplatin and irinotecan (see figure 7). Clinical Experts state that it is important to have access not only to cetuximab combination treatment but also cetuximab monotherapy as the relatively mild toxic effects seen with cetuximab monotherapy (Cunningham et al 2004; Appendix 1) coupled with its clinical efficacy make it an option for patients who are not considered candidates for further treatment with irinotecan-based chemotherapy or who choose not to receive such treatment. The choice of combination therapy versus monotherapy will need to be made on a patient-by-patient basis.

Based upon the NICE costing template for NICE TA 176, the proportion of KRAS wild-type mCRC patients who express EGFR, and clinical opinion, it has been estimated that 256 to 385 patients are eligible for treatment with cetuximab in the third line setting.

1.3 The decision problem

The comparators to cetuximab as designated by the final scope are bevacizumab and panitumumab, as well as best supportive care the current standard of care within the NHS for third line metastatic colorectal cancer. As there is a lack of published clinical data describing the treatment effect of bevacizumab for KRAS wild-type patients in the third line setting, it is felt that bevacizumab is not appropriate comparator in this appraisal.

This submission will demonstrate the effectiveness and cost-effectiveness of cetuximab versus panitumumab and best supportive care for patients expressing the KRAS wild type gene.

One further consideration in the decision problem is the application of supplementary advice for appraising "*End of Life"* treatment in this setting. The criteria for applying the supplementary advice are listed in the box below:

The supplementary advice for appraising end of life treatment consists of the following three criteria:
1. *There is sufficient evidence to indicate that the treatment offers an extension of life (≥ 3 months);*
2. *Treatment is indicated for patients with a short life-expectancy (less than 24 months);*
3. *The treatment is indicated for small populations.*

The life expectancy of patients with unresectable metastatic colorectal cancer is below 24 months, and this submission will outline evidence showing cetuximab offers an extension of life of more than 3 months within this setting, both in combination with chemotherapy and as monotherapy. In the third line setting where there is an absence of therapeutic options providing similar survival benefit used within the NHS, cetuximab also improves quality of life compared to BSC (Au et al 2009). This evidence alongside the small population eligible for cetuximab treatment on the NHS, indicates that the End of life criteria are applicable.

1.4 Clinical Evidence

Pivotal Studies

The BOND study is the pivotal RCT evaluating the efficacy of cetuximab in combination with chemotherapy versus cetuximab monotherapy, on which the original license for metastatic colorectal cancer was based; however this was prior to the identification of the KRAS oncogene as a predictive biomarker. It was an open-label, randomised, multicentre phase II study of cetuximab in combination with irinotecan versus cetuximab monotherapy in patients with histologically confirmed colorectal adenocarcinoma expressing EGFR. 329 individuals were randomised to receive treatment.

The median time to progression was significantly greater in the combination-therapy group compared to the cetuximab monotherapy group (4.1 month vs 1.6 months; $p< 0.01$). The improvement in median

overall survival of 8.6 months in the combination-therapy group versus 6.9 months in the monotherapy group.

The CO17 study is the pivotal phase III multicentre, open-label randomised controlled trial designed to investigate the use of cetuximab in combination with best supportive care (BSC) compared with BSC alone in patients with EGFR-expressing metastatic colorectal cancer.

The difference in overall survival between cetuximab plus BSC and BSC increased significantly when those participants bearing KRAS wild-type oncogene were analysed. The addition of cetuximab to BSC significantly increased progression free survival from 1.9 months to 3.7 months (HR=0.77; p=0.005) and overall survival from 4.8 months to 9.5 months (HR=0.55; p<0.01).

Systematic Review

A systematic review was undertaken to identify any additional RCTs evaluating the efficacy of cetuximab or any relevant comparators (including other targeted therapies) in the pre-treated KRAS wild-type mCRC population. The only additional relevant trial identified was an open-label phase III randomised controlled trial designed to investigate the use of panitumumab compared with BSC alone in patients with EGFR-expressing metastatic colorectal cancer who had been previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin (Van Cutsem et al 2007).

A KRAS analysis of the study participants to determine whether the mutation status of the KRAS gene modified the treatment effect of panitumumab on efficacy has also been conducted and published (Amado et al. 2008). The difference between panitumumab versus BSC on PFS was significantly greater among patients with KRAS wild-type disease compared with patients with KRAS mutant disease, No statistically significant OS difference was observed between treatment arms among all patients (or in either of the KRAS groups).

Non randomised studies and Real World Data

In order to understand the real world use of cetuximab and in the absence of RCT evidence for cetuximab in combination with chemotherapy in the pre-treated KRAS wild-type mCRC population, a systematic review of non RCTs was also undertaken. Twenty-eight studies were retrieved from the literature review, which included only one comparative study (De Roock et al, 2008) within the KRAS wild-type population that could be used to assess comparative clinical and cost-effectiveness.

De Roock et al 2008 is a retrospective analysis of four clinical studies reporting outcomes by KRAS status. Progression free survival and overall survival was more favourable in the KRAS wild-type population for patients who received cetuximab in combination with chemotherapy compared to monotherapy (PFS: 34 weeks vs. 12 weeks; p=0.016 / OS: 45 weeks vs. 27 weeks; p<0.01).

As the De Roock et al 2008 study only included a small number of patients, we used the largest cohort study identified in the literure review to confirm the treatment effect of cetuximab plus irinotecan based chemotherapy (De Roock et al, 2010).

These results provide additional evidence that KRAS is a predictive biomarker of cetuximab response (in combination with chemotherapy and as monotherapy) for patients with mCRC who have received at least two previous chemotherapy regimens. The studies can also be used in an indirect treatment comparison to compare the clinical effectiveness of cetuximab in combination with chemotherapy within the KRAS wild type population against best supportive care and panitumumab in the absence of a RCT.

Indirect Treatment Comparisons

The CO.17 trial shows that cetuximab monotherapy is beneficial compared to standard best supportive care in improving progression free survival and overall survival. To assess comparative clinical effectiveness of cetuximab in combination with chemotherapy against panitumumab or BSC and cetuximab monotherapy against panitumumab, indirect treatment comparisons have to be constructed using the De Roock et al studies, CO.17 and the Amado et al (2008) study. In all

analyses cetuximab combination therapy has a beneficial effect on overall survival against the comparator. These results are pivotal to the favourable comparative cost-effectiveness analyses.

1.5 Cost-effectiveness

- A de novo Markov model (executed in Microsoft Excel) was developed to inform the comparative cost effectiveness of the following comparisons of treatments for patients with EGFR-expressing, KRAS wild-type mCRC who have failed at least two chemotherapeutic regimens in the metastatic setting;
  - Cetuximab plus best supportive care (BSC) versus BSC
  - Cetuximab plus irinotecan versus BSC
  - Cetuximab plus BSC versus panitumuab plus BSC;
  - Cetuximab in combination with irinotecan versus panitumumab plus BSC.
- The model estimates costs from the perspective of the NHS in the UK, and health outcomes both in terms of life-years gained (LYG) and incremental quality-adjusted life-years (QALYs) for the different therapies across a life time time horizon.
- The model is based upon three health states: progression free (PF), progressive disease (PD) and death. The outcomes for progression-free survival and overall survival are extracted from the published literature and subsequently adjusted by quality of life, resource use and costs.
- The clinical evidence is used to account for progression free survival and overall survival in the model and therefore drive the proportion of patients in the three health states. The model uses Kaplan-Meier data to estimate the lifetime mean overall survival and progression-free survival. which were derived either from patient-level data where it was available (Cetuximab plus BSC vs. BSC) or from the published progression-free and overall survival Kaplan-Meier estimates.
- The utilities used were collected using the generic preference based measure HUI scale in the CO.17 study. Access to patient level data allowed utility values to be estimated for cetuximab plus BSC and BSC in progression free and progressive disease health states. In the absence of evidence the utility values for cetuximab plus irinotecan and panitumumab plus BSC were assumed to be equivalent as cetuximab monotherapy but this was explored in the sensitivity analysis.
- Resource use and costs in the model include cost of chemotherapy drugs acquisition, cost of administration, cost of KRAS test, cost of best supportive care, and costs of adverse events.
- Extensive univariate sensitivity and scenario analyses in addition to probabilistic sensitivity analysis were employed to test the robustness of the base case approach.

Results

I) Cetuximab plus best supportive care vs. best supportive care

Table E1: Summary of base case results for cetuximab plus BSC versus BSC.

Comparators	Total costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALY	ICER £/QALY	*EoL criteria*	
								Weighted QALY for £20,000 threshold	***Weighted QALY for £30,000 threshold***
BSC	£7,580	0.512	0.359						
Cetuximab plus BSC	£21,836	0.829	0.662	£14,256	0.317	0.303	**£47,095**	2.35	**1.57**

- Cetuximab plus BSC has a 67% chance of being the cost-effective option at the £50,000 willingness to pay threshold.

- Further scenario analyses were explored which showed that the CO.17 bottom up costing (£39,000 per QALY gained) and vial sharing (which is likely to be common practice in chemotherapy units in specialist centres) had favourable effects on the ICER.

II) Cetuximab plus irinotecan vs. best supportive care

Table E2: Summary of base case results for cetuximab plus irinotecan versus BSC

Comparators	Total costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALY	ICER £/QALY	*EoL criteria*	
								Weighted QALY for £20,000 threshold	***Weighted QALY for £30,000 threshold***
BSC	£5,149	0.547	0.391						
Cetuximab plus irinotican	£37,248	1.325	1.059	£31,976	0.779	0.668	**£43,887**	2.19	**1.46**

- Cetuximab plus irinotecan has a 45% chance of being the cost-effective option at the £40,000 willingness to pay threshold and a 68% chance at the £50,000 threshold.
- Further scenario analyses were explored which showed that the CO.17 bottom up costing (£33,000 per QALY gained) and vial sharing (which is likely to be common practice in chemotherapy units in specialist centres) had favourable effects on the ICER.

III) Cetuximab plus best supportive care vs. panitumumab plus best supportive care

Table E3: Summary of base case results for cetuximab plus BSC versus panitumumab plus BSC

Comparators	Total costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALY	ICER £/QALY
Panitumumab plus BSC	£24,465	0.585	0.469				
Cetuximab plus BSC	£21,836	0.829	0.662	£574	0.244	0.193	**Dominant**

- Cetuximab plus BSC has a 100% chance of being the cost-effective option at the £15,000 willingness to pay threshold.

IV) Cetuximab plus irinotecan vs. panitumumab plus best supportive care

Table E4: Summary of base case results for cetuximab plus irinotican versus panitumumab plus BSC

Comparators	Total costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALY	ICER £/QALY
Panitumumab plus BSC	£23,810	0.551	0.443				
Cetuximab plus irinotican	£37,248	1.325	1.059	£13,438	0.774	0.616	**£21,819**

- Cetuximab plus irinotecan has a 74% chance of being the cost-effective option at the £30,000 willingness to pay threshold and an 89% chance at the £40,000 threshold.

Summary

The end of life criteria is applicable in this setting as there is a small population eligible for cetuximab treatment on the NHS, and cetuximab extends survival by more than three months in a population whose median survival is less than 24 months.

On this basis cetuximab plus irinotecan and cetuximab plus BSC for the treatment of EGFR-expressing, KRAS wild-type mCRC patients who have received at least two previous chemotherapeutic regimens in the metastatic setting represents a cost-effective use of NHS resources.

1.7 Wider Implications of the Technology

Based upon the estimate that between 260 and 390 individuals are eligible for treatment with cetuximab in the third line setting, an uptake of between 30% and 90% over the first five years following the NICE guidance, and 80% of the patients being prescribed cetuximab in combination with chjemotherapy, the net resource implications for England and Wales would be between £1.5 million and £2.3 million in year 1 and between £4.8 million and £7.5 million in year 5.