cetuximab, 100mg/20mL and 500mg/100mL solution for intravenous infusion (Erbitux®) No. (543/09)
Merck Serono Ltd

06 March 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

cetuximab (Erbitux®) is not recommended for use within NHS Scotland for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer in combination with chemotherapy.

Outcomes for patients with KRAS wild-type disease were derived from retrospective, post hoc analyses of one phase II and one phase III study. Both these analyses showed an increase in overall response rate and a small, but statistically significant, increase in median progression free survival time when cetuximab was added to standard first-line chemotherapy.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of patients with epidermal growth factor receptor (EGFR)-expressing, Kirsten rat sarcoma (KRAS) wild-type metastatic colorectal cancer in combination with chemotherapy.

Dosing information

First infusion dose is 400mg cetuximab per m^2 body surface area (BSA), then subsequent weekly doses of 250mg/m^2 until disease progression.

Prior to the first infusion, patients must receive pre-medication with an antihistamine and a corticosteroid. This is recommended prior to all subsequent infusions.

Dose modifications may be required for concomitantly used chemotherapeutic agents. These must not be administered earlier than one hour after the end of the cetuximab infusion.

Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. 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.

Product availability date

24 September 2008

Summary of evidence on comparative efficacy

Cetuximab is a chimeric monoclonal antibody that blocks the epithelial growth factor receptor (EGFR), thus inhibiting the proliferation of cells dependent on EGFR activation for growth. EGFR over-expression is common in a wide variety of tumours. KRAS is an oncogene that encodes for the protein K-Ras, which is involved primarily in regulating cell division. Somatic mutation of the KRAS gene leads to a K-Ras protein which is always active and can lead to uncontrolled cell division. Patients with a KRAS mutation are likely to be resistant to cetuximab.

Evidence to support the use of cetuximab in combination with chemotherapy in the first-line treatment of EGFR-expressing metastatic colorectal cancer is from one phase ll and one phase lll study.. Patients recruited to these studies were ≥18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and histologically confirmed adenocarcinoma of the colon or rectum, with a first occurrence of bi-dimensionally measurable metastatic disease (not curatively resectable). Both studies were of open-label design; however the primary outcomes were determined by a blinded review of the source data by an Independent Review Committee. Randomisation was stratified for ECOG status and region. In both studies, KRAS status was established in a post-hoc analysis requested by the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMEA). As the marketing authorisation was subsequently restricted to patients with KRAS wild-type disease, the study results presented will be limited to this population. In this submission the company has proposed a further restriction to use in patients not previously treated and with metastatic disease confined to the liver.

A total of 337 patients with EGFR-expressing metastatic colorectal cancer were included in the final analysis set in the phase ll study. Of these, 134 patients had KRAS wild-type disease and had been randomised to either FOLFOX-4 (5-fluorouracil (5-FU) 400mg/m² bolus, followed by a 22-hour continuous infusion of 5-FU 600mg/m² and folinic acid (FA)

200mg/m^2 infusion on Day 1 and 2, plus oxaliplatin 85mg/m^2 infusion on Day 1, every two weeks) (n=73) or FOLFOX-4 plus cetuximab (400mg/m^2 infusion on Day 1 then a 250mg/m^2 infusion every seven days thereafter) (n=61). Patients were treated until disease progression or unacceptable toxicity. The primary outcome was the response rate in the intention to treat (ITT) population, classified according to the modified World Health Organisation (WHO) criteria and defined as the proportion of patients achieving a confirmed complete response (CR) or partial response (PR) as best overall response according to radiological assessments. Secondary outcomes included progression free survival (PFS) time.

The response rate was significantly improved in the FOLFOX-4 plus cetuximab group compared to the FOLFOX-4 alone group, 61% (95% confidence interval (CI): 47 to 73) versus 37% (95% CI: 26 to 49), respectively. The median PFS was also significantly longer in the FOLFOX-4 plus cetuximab group: 7.7 months (95% CI: 7.1 to 12) versus 7.2 months (95% CI: 5.6 to 7.4), giving a hazard ratio (HR) of 0.57 (95% CI: 0.36 to 0.91). Six patients (9.8%) in the cetuximab group had metastatic surgery of curative intent compared with three (4.1%) in the FOLFOX-4 alone group. A subgroup analysis was performed in 38 patients whose metastatic disease was confined to the liver. Outcomes for this patient group were not reported.

A total of 1,198 EGFR-expressing metastatic colorectal cancer patients were included in the final analysis set in the phase lll study. Of these, 348 patients had KRAS wild-type disease and had been randomised to either FOLFIRI (5-FU 400mg/m^2 bolus followed by a 46-hour continuous infusion of 2,400mg/m^2, FA 400mg/m^2 (racemic) or 200mg/m^2 (L-form) plus irinotecan 180mg/m^2 infusion, all on Day 1 every two weeks) (n=172) or FOLFIRI plus cetuximab (400mg/m^2 infusion on Day 1 then a 250mg/m^2 infusion every seven days) (n=176). Patients were treated until disease progression or the occurrence of unacceptable adverse events. The primary outcome was the PFS time in the ITT population, 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 outcomes included response rate, as measured by the modified WHO criteria and defined as the proportion of patients achieving a confirmed complete response (CR) or partial response (PR) as best overall response according to radiological assessments.

The median PFS time was significantly longer in the FOLFIRI plus cetuximab group compared to the FOLFIRI alone group: 9.9 months (95% CI: 8.7 to 15) versus 8.7 months (95% CI: 7.4 to 9.9), giving an HR of 0.68 (95% CI: 0.50 to 0.93). The response rate was also significantly improved in the FOLFIRI plus cetuximab group: 59% (95% CI: 52 to 67) versus 43% (95% CI: 36 to 51), respectively, but there was no difference in the number of patients having metastatic surgery with curative intent (three patients (1.7%, 3/172) versus two patients (1.1%, 2/176), respectively.

A subgroup analysis was undertaken in 67 patients whose metastatic disease was confined to the liver. The median PFS time was further extended in this small group of patients but the difference between the treatment arms did not reach significance, 14.6 months in the FOLFIRI plus cetuximab group and 9.5 months in the FOLFIRI alone group (p=0.44), HR 0.72 (95% CI: 0.32 to 1.64). The difference in response rate between the groups was significant (77% versus 50% for FOLFIRI plus cetuximab versus FOLFIRI alone), but there was no difference in the number of patients having metastatic surgery with curative intent (two patients versus one patient, respectively).

Summary of evidence on comparative safety

The safety profile seen in the clinical studies was comparable with the known safety profile of cetuximab. The European Public Assessment Report (EPAR) states that cetuximab has a non-trivial safety profile and that there is a suggestion that there is an increased risk of death in patients receiving cetuximab as add-on to chemotherapy.

The addition of cetuximab to FOLFOX-4 increased the incidence of any Grade 3 or 4 adverse events in the KRAS wild-type population (84% vs 63%), notably increases in diarrhoea (12% versus 6%) and neutropenia (41% versus 33%). When cetuximab was added to FOLFIRI the incidence of any Grade 3 or 4 adverse events increased in the KRAS wild-type population (78% versus 51%), in particular diarrhoea (17% versus 9%) and neutropenia (25% versus 17%).

Summary of clinical effectiveness issues

At the time of recruiting for the two above studies, the data supporting KRAS mutational status as a predictive marker for EGFR-targeted therapies was not confirmed, nor was the extent of resistance to cetuximab therapy in patients with a somatic KRAS mutation. The necessary post-hoc analysis for KRAS wild-type disease has significantly reduced the study population. The further restriction of this population to patients in whom metastatic disease is confined to the liver means that the population under consideration consists of 38 patients from the phase ll study and 67 from the phase lll study. Although the baseline characteristics between the arms in the two studies remained balanced for the KRAS wild-type population, whether this remains true for the population with liver metastases only is not known.

The primary outcome of PFS time in the phase lll study, in the KRAS wild-type population, is statistically significantly longer with the FOLFIRI plus cetuximab combination. It is difficult to assess whether the clinical benefit of an additional 1.2 months of PFS time is significant when the exacerbated adverse event profile and additional weekly drug administration, which may require an extra weekly hospital visit, is taken into consideration. In patients with metastases confined to the liver, the difference in PFS time between the study groups was not significant, although it was prolonged in both arms. There was no difference in the number of patients having metastatic surgery with curative intent either in the KRAS wild-type population or in the sub-population with metastases confined to the liver. In the phase ll study, the difference in PFS time between the different arms was further reduced to 0.5 of a month, although in this study, twice as many patients had metastatic surgery with curative intent in the cetuximab combination group. There were no reported outcomes for the population of patients with metastases confined to the liver.

The company has stated that cetuximab in addition to chemotherapy is likely only to be used in a younger, fitter population. This is reflected in the two clinical studies. In the KRAS wild-type population, the median age was 59 to 61 years, with approximately two thirds of the population being less than 65 years old, and almost 90% of patients having an ECOG performance status of 0 or 1. The median age at diagnosis of colorectal cancer in the UK is >70 years with many patients presenting with metastatic disease and having poorer performance status, so this treatment is expected only to be appropriate for a small proportion of the metastatic colorectal cancer population.

A phase II study presented in the submission and used in the economic model to estimate liver resection rates in the population with metastases confined to the liver, following treatment with cetuximab plus FOLFOX or cetuximab plus FOLFIRI, has not been discussed

here as it was an uncontrolled study of neo-adjuvant treatment, undertaken in Austria and Germany, the evidence in the KRAS wild-type population was a post-hoc analysis and as cetuximab was included in both arms of the study this was a comparison of the FOLFOX and FOLFIRI regimens and not cetuximab. Scottish and UK experts suggest that the liver resection rate in this population following standard chemotherapy is likely to be between 20 and 30%.

There will be an additional cost and requirement for a reliable laboratory test for the identification of KRAS mutational status. The Summary of Product Characteristics recommends that the detection of KRAS mutational status be performed by an experienced laboratory using a validated test method.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility Markov model with a weekly cycle and a ten year horizon. The modelling was undertaken for the patient subset with KRAS wild type and metastases confined to the liver. This compared cetuximab+FOLFOX-4 with FOLFOX-4 and cetuximab+FOLFIRI with FOLFIRI. During these first-line therapies patients could be resected with curative intent at 16 weeks. Progression of disease led to second-line FOLFOX-6 or FOLFIRI, with further progression leading to treatment with best supportive care.

The rates of death prior to progression and progression free survival for first-line therapies were estimated from the studies with an active control. The rates of liver resection for the first-line cetuximab containing regimens were drawn from the phase II neo-adjuvant study examining the possibility of resection. The rates of liver resection for the non-cetuximab containing regimens were estimated from a separate published study which reported resection rates in patients treated with conventional chemotherapy. The modelling of time to progression from second-line therapies was also taken from this paper, while a third paper was used to project survival under best supportive care. Survival after resection was drawn from a fourth paper.

Quality of life values were estimated from EQ-5D data in first-line patients and health utilities index (HUI) data in third-line treated patients. Resource use was mainly drawn from the controlled trials, and valued using standard sources.

For the FOLFOX-4 comparison, cetuximab was estimated to increase costs by £17,730 and result in a gain of 0.52 QALYs to yield a cost effectiveness of £33,780 per QALY. For the FOLFIRI comparison, cetuximab was estimated to increase costs by £18,353 and result in a gain of 0.65 QALYs to yield a cost effectiveness of £28,024 per QALY. The results were very sensitive to the assumed rates of resection.

Weaknesses included:

- the use of varied sources for the clinical inputs, with progression free survival being drawn from the trials with active controls, but resection rates for cetuximab being drawn from the separate phase II trial that had the express aim of assessing the possibility of resection (and these rates were considerably higher than those shown in the pivotal studies);
- the resection rates for the non-cetuximab comparators being drawn from a paper within the literature which will probably underestimate resection rates for those with liver metastases confined to the liver as the study was not solely of patients with metastases confined to the liver;

- not applying the same logic in mapping response rates to resection rates, to both the cetuximab regimens and the non-cetuximab regimens;
- not considering the impact of the safety profile of cetuximab and adverse events upon quality of life;
- some lack of transparency in drug use costing with duration of cetuximab treatment being assumed rather than derived from the model outputs;
- sensitivity analyses which did not sufficiently explore the key clinical inputs to the model such as resection rates, resection failure rates and treatment stopping rules;

As a consequence, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:
- Beating Bowel Cancer
- Bowel Cancer UK

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 67, Management of Colorectal Cancer; a national clinical guideline in March 2003. A review report in 2007 indicated that the guideline may require revision in the light of new evidence.

National Institute for Health and Clinical Excellence (NICE) published a cancer service guideline in 2004 entitled “Improving outcomes in colorectal cancer”.

National Comprehensive Cancer Network (NCCN) – Clinical practice guidelines in oncology (Colon Cancer), V.3.2008.

Guidelines for the management of colorectal cancer. Association of Coloproctology of Great Britain and Ireland 2007.

Cost of relevant comparators

NICE has recommended a number of different regimens for metastatic colorectal cancer or advanced colorectal cancer including capecitabine, tegafur/uracil plus folinic acid, oxaliplatin/fluorouracil/folinic acid and irinotecan/fluorouracil/folinic acid. SMC experts suggested that capecitabine/oxaliplatin (XELOX), FOLFOX-4, and capecitabine alone are being used in Scotland for the treatment of metastatic colorectal cancer.

Name of regimen	Details of regimen	Cycle length	Cost per cycle (£)	Cost per 26 weeks (£)
cetuximab + FOLFOX-4	**cetuximab 400mg/m^2 iv infusion for 1st dose, then 250mg/m^2 thereafter, D1 and D8 oxaliplatin 85mg/m^2 iv infusion, D1 folinic acid 200mg/m^2 iv infusion, D1-2 fluorouracil 400mg/m^2 iv bolus then**	**2 weeks**	**2582**	**32291**

	600mg/m^2 iv infusion, D1-2			
cetuximab + FOLFIRI	**cetuximab 400mg/m^2 iv infusion for 1st dose, then 250mg/m^2 thereafter, D1 and D8 irinotecan 180mg/m^2 iv infusion, D1 folinic acid 400mg/m^2 iv infusion, D1 fluorouracil 400mg/m^2 iv bolus then 2400mg/m^2 iv infusion, D1**	**2 weeks**	**2331**	**29808**
FOLFOX-4	oxaliplatin 85mg/m^2 iv infusion D1 fluorouracil 400mg/m^2 iv bolus 600mg/m^2 iv infusion D1, 2 folinic acid 200mg/m^2 iv infusion D1, 2	2 weeks	922	12,116
FOLFIRI	irinotecan 180mg/m^2 iv infusion, D1 folinic acid 400mg/m^2 iv infusion, D1 fluorouracil 400mg/m^2 iv bolus then 2400mg/m^2 iv infusion, D1	2 weeks	741	9633
XELOX	oxaliplatin 130mg/m^2 iv infusion, D1 capecitabine 1000mg/m^2 orally twice daily, D1-14	3 weeks	1073	8584
XELIRI	irinotecan 250mg/m^2 iv infusion, D1 capecitabine 1000mg/m^2 orally twice daily, D1-14	3 weeks	874	6992
De Gramont	fluorouracil 400mg/m^2 iv bolus then 600mg/m^2 iv infusion, D1-2 folinic acid 200mg/m^2 iv infusion, D1-2	2 weeks	239	3109
capecitabine	capecitabine 1250mg/m^2 orally twice daily, D1-14	3 weeks	310	2482

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 05 Jan 2009. D = day

Note that the racemic form of folinic acid was used, where appropriate. Costs are based on a body surface area of 1.8m^2. Costs per 26 weeks are calculated for complete cycles administered during this period.

Additional information: budget impact

The manufacturer's estimates were based on the assumed numbers of patients with EGFR-expressing, KRAS wild type colorectal cancer not previously treated and with metastatic disease confined to the liver. Based on a population of 3,797 patients with colorectal cancer, the manufacturer estimated that 218 patients would be eligible for treatment in year one, rising to 228 patients by year five. Given an initial market share of 20% in year one rising to 80% by year five, this resulted in a gross drug cost of £642k in year one rising to £2.7million by year five.

There would also be additional drug administration costs due to increased frequency of infusions, of £83k in year 1 rising to £349k by year 5 resulting in an overall total by year 5 of around £3million. The costs of KRAS testing were not taken into account in the budget impact estimates.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 February 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

Those undernoted references, shaded grey, are additional to those supplied with the submission.

KRAS. Genetics Home Reference. http://ght.nlm.nit.gov/gene=kras

The European Medicines Agency (EMEA) European Public Assessment Report. Cetuximab EMEA/H/C/000558/II/0020 http://www.emea.europa.eu/humandocs/PDFs/EPAR/erbitux/H-558-11-26-AR.pdf