

**cetuximab, 100mg/20mL and 500mg/100mL solution for intravenous infusion (Erbix<sup>®</sup>)** **No. (543/09)**  
**Merck Serono Ltd**

15 January 2010

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 resubmission

**cetuximab (Erbix<sup>®</sup>)** is accepted for restricted use within NHS Scotland for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, Kirsten rat sarcoma (KRAS) wild-type metastatic colorectal cancer in combination with chemotherapy.

Post hoc analyses from one phase III and one phase II study in patients with KRAS wild-type status who had not previously received chemotherapy for metastatic disease, 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 combination chemotherapy.

Cetuximab is restricted to use in patients who have not previously received chemotherapy for their metastatic disease, with liver metastases only that are considered non-resectable but in whom potentially curative liver metastasis resection would be undertaken if the lesions became resectable after treatment with chemotherapy and cetuximab.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of cetuximab. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

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 dose is 400mg per m<sup>2</sup> body surface area (BSA) once weekly and should be administered intravenously (iv) over 120 minutes. Subsequent weekly doses are 250mg per m<sup>2</sup> BSA and are recommended to be administered over 60 minutes. The infusion rate must not exceed 10mg/min. Treatment should be continued 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. They 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**

17 July 2008

**Summary of evidence on comparative efficacy**

Cetuximab is a chimeric monoclonal antibody that blocks the EGFR, thus inhibiting the proliferation of cells dependent on EGFR activation for growth. The KRAS gene, an oncogene, encodes for the protein K-Ras which is involved primarily in regulating cell division and is a central down-stream signal-transducer of EGFR. Extensive data now demonstrate that use of cetuximab should be restricted to patients with tumours not harbouring activating KRAS mutations.

In metastatic colorectal cancer (mCRC), in up to 50% of patients the liver may be the only site of spread. The 5-year survival rate for mCRC is 12%.

The submitting company has requested that SMC review a niche within the licensed indication specifically for patients who have not previously received chemotherapy for their metastatic disease. The efficacy and safety data presented reflects this niche.

Efficacy was determined from two studies of similar design; one phase III and one phase II. Data for the full analysis set were presented for both studies. However, the main data in the submission focused on the post hoc analysis of the KRAS wild-type subgroup, which was requested by the regulatory agencies and reflects the marketing authorisation.

Both studies were open-label, randomised and multicentre. Patients were  $\geq 18$  years with presence of histologically confirmed adenocarcinoma of the colon or rectum which expressed EGFR. Patients had first occurrence of metastatic disease which was not curatively resectable with at least 1 bi-dimensionally measurable index lesion. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$  and a life expectancy of at least 12 weeks. Patients were required to have recovery from relevant toxicity to previous treatment and have adequate haematological, hepatic and renal function. In both studies, patients were treated until progressive disease was diagnosed or unacceptable toxicity occurred.

The phase III study recruited 1,198 patients who were randomised in a 1:1 ratio to cetuximab ( $400\text{mg}/\text{m}^2$  infusion on Day 1 then a  $250\text{mg}/\text{m}^2$  infusion every seven days thereafter) plus FOLFIRI (5-fluorouracil (5-FU)  $400\text{mg}/\text{m}^2$  bolus followed by a 46-hour continuous infusion of  $2,400\text{mg}/\text{m}^2$ , folinic acid (FA)  $400\text{mg}/\text{m}^2$  (racemic) or  $200\text{mg}/\text{m}^2$  (L-form) plus irinotecan  $180\text{mg}/\text{m}^2$  infusion, all on Day 1 every two weeks) or FOLFIRI alone. In the KRAS wild-type sub-group, 172 patients received cetuximab plus FOLFIRI and 176 patients received FOLFIRI alone. The primary outcome was progression free survival (PFS) in the intention-to-treat (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 and overall survival. At baseline, the median age of patients with KRAS wild-type status was approximately 60 years, with an ECOG status mainly of 0 (58%) or 1 (38%). Median duration of mCRC was 1.6 months and 22% of patients had received prior adjuvant chemotherapy.

In the KRAS wild-type population the median PFS was significantly longer in the cetuximab plus FOLFIRI group compared with the FOLFIRI alone group: 9.9 months (95% Confidence Interval (CI): 8.7 to 14.6) versus 8.7 months (95% CI: 7.4 to 9.9), hazard ratio (HR) 0.68 (95% CI: 0.50 to 0.93). The response rate was also significantly improved in the cetuximab plus FOLFIRI group: 59% (95% CI: 52 to 67) versus 43% (95% CI: 36 to 51), but there was no significant difference between the groups in the rate of metastatic surgery of curative intent: 3 (1.7%) patients in cetuximab plus FOLFIRI group and 2 (1.1%) patients in the FOLFIRI alone group. There was no significant difference in overall survival between the groups: 24.9 months in the cetuximab plus FOLFIRI group versus 21 months in the FOLFIRI alone group; median follow-up for 30 months (HR=0.84, 95% CI: 0.64 to 1.11).

A subgroup analysis was performed for the 67 patients whose metastatic disease was confined to the liver. The median PFS times were extended further to 14.6 months (95% CI: 9.1 to unknown) in the cetuximab plus FOLFIRI group and 9.5 months (95% CI: 7.4 to 11.1) in the FOLFIRI alone group but the difference was not significant, HR 0.72 (95% CI: 0.32 to 1.64). The response rate was significantly improved with the addition of cetuximab (77% versus 50%) but there was no significant difference between the groups in the number of patients having metastatic surgery of curative intent; two patients (5.7%,  $n=2/35$ ) in the cetuximab plus FOLFIRI group and one patient (3.1%,  $n=1/32$ ) in the FOLFIRI alone group.

The phase II study recruited 337 patients who were randomised in a 1:1 ratio to cetuximab ( $400\text{mg}/\text{m}^2$  infusion on Day 1 then a  $250\text{mg}/\text{m}^2$  infusion every seven days thereafter) plus FOLFOX-4 (5-FU  $400\text{mg}/\text{m}^2$  bolus, followed by a 22-hour continuous infusion of  $600\text{mg}/\text{m}^2$  and FA  $200\text{mg}/\text{m}^2$  infusion on Days 1 and 2, plus oxaliplatin  $85\text{mg}/\text{m}^2$  infusion on Day 1, every two weeks) or FOLFOX-4 alone. In the KRAS wild-type sub group, 61 patients received cetuximab plus FOLFOX-4 and 73 patients received FOLFOX-4 alone. The primary outcome was response rate in the ITT population, defined as the proportion of patients having achieved confirmed complete response (CR) or partial response (PR) as best overall response according to radiological assessments. Secondary outcomes included PFS and overall survival. At baseline the median age of patients with KRAS wild-type status was 59

years, with an ECOG status mainly of 0 (34%) or 1 (55%). Median duration of mCRC was 1.4 months and 15% of patients had received prior adjuvant chemotherapy.

In the KRAS wild type population, the response rate was significantly improved in the cetuximab plus FOLFOX-4 group compared with FOLFOX-4 alone group, 61% (95% CI: 47 to 73) versus 37% (95% CI: 26 to 49) respectively. The median PFS was also significantly longer in the cetuximab plus FOLFOX-4 group compared with the FOLFOX-4 alone group: 7.7 months (95% CI: 7.1 to 12) versus 7.2 months (95% CI: 5.6 to 7.4), HR 0.57 (95% CI: 0.36 to 0.91). Metastatic surgery of curative intent was performed in seven patients (11.5%) in the cetuximab plus FOLFOX-4 group (n=6/7 achieved R0 resection (microscopic clearance)) and three patients (4.1%) in the FOLFOX-4 alone group (n=3/3 achieved R0 resection); all had liver metastases. Survival data are immature.

A subgroup analysis was performed for the 38 patients whose metastatic disease was confined to the liver. Outcomes for this patient group were not reported.

### **Summary of evidence on comparative safety**

The safety profile of cetuximab observed in both pivotal studies was comparable with the known adverse reaction profile. Cetuximab has a non-trivial safety profile and data are compatible with an increased risk of death in patients administered cetuximab as add-on to chemotherapy.

In the phase III study, KRAS wild-type population, grade 3 or 4 adverse events were more frequent with cetuximab plus FOLFIRI (78%) than with FOLFIRI alone (51%) and included skin reactions (rash, paronychia and acneiform dermatitis; 19% versus 0%), neutropenia (25% versus 17%), and diarrhoea (17% versus 9.1%).

In the phase II study, KRAS wild-type population, grade 3 or 4 adverse events were more frequent with cetuximab plus FOLFOX-4 (84%) than with FOLFOX-4 alone (63%) and included rash (12% versus 0%), neutropenia (41% versus 33%) and diarrhoea (12% versus 5.5%).

### **Summary of clinical effectiveness issues**

The submitting company has requested that SMC review a niche within the licensed indication specifically for patients who have not previously received chemotherapy for their metastatic disease. The efficacy and safety data presented in this submission reflects this niche but the economic case concentrates on patients within the above group with liver only metastases that are considered non-resectable but that may become amenable to potentially curative liver resection after responding to chemotherapy plus cetuximab.

At the time the study was designed, the therapeutic benefits of cetuximab in KRAS wild-type patients was unknown although it is now accepted that monoclonal antibody EGFR inhibition should be limited to these patients. The efficacy analyses were performed post-hoc on a subset of the initially conceived population for these studies in collaboration with regulatory agencies and hence the analysis is likely to be underpowered. Power was further reduced when analyses was undertaken in the KRAS wild-type population with liver metastases. In general the baseline characteristics between the full analyses set and the KRAS wild-type subset were similar for both studies but unknown for the population with only liver metastases.

Both studies were open-label. Blinding was not a practical option because many subjects treated with cetuximab can be readily identified by skin reactions, however the primary endpoints of both studies were determined by a blinded review of the source data by an Independent Review Committee.

Response rates in both studies were significantly improved with cetuximab. However the improvement in median PFS in the KRAS wild-type population when cetuximab was added to FOLFIRI and FOLFOX-4 was 1.2 months and 0.5 months respectively and therefore limited. These clinical benefits should be considered against the added toxicity of cetuximab when administered as add-on chemotherapy and the practicalities for the patient to receive cetuximab weekly in addition to the fortnightly administered FOLFOX or FOLFIRI. Additionally the difference in the overall survival between the groups in the phase III study was not significant and in the phase II study was unknown.

The submitting company advise that combination therapy of cetuximab plus FOLFIRI or FOLFOX-4 is expected to be appropriate for younger, fitter patients, comparable to the populations in the two pivotal studies. In the UK the median age of diagnosis of CRC is over 70 years and targeting patients with a lower mean age and higher performance status than the average for the whole of the CRC population may preclude administration to many CRC patients.

Quality of life (QoL) was assessed in the phase III study in both the primary and KRAS wild-type populations with particular attention to the effects of treatment on global health status and social functioning. There were no significant differences between the groups in any of the QoL scale scores when analysed according to changes from baseline levels. In particular cetuximab induced acne-like rash did not significantly affect the social functioning scale. No QoL data was collected from the phase II study.

The use of cetuximab in this setting requires the additional histological analysis of tumour samples, to ascertain whether they express EGFR and are KRAS wild-type. The SPC notes that it is recommended that the detection of KRAS mutational status be performed by an experienced laboratory using a validated test method. This will incur an additional cost.

### **Summary of comparative health economic evidence**

The manufacturer submitted a lifetime cost-utility analysis of the addition of cetuximab to either the FOLFOX or FOLFIRI chemotherapy regimens. The manufacturer niched the economic analysis to patients whose metastatic disease is confined to the liver and is currently unresectable but which may become amenable to potentially curative liver resection after responding to chemotherapy plus cetuximab. Patients should have KRAS wild-type disease, good performance status and be suitable for irinotecan- or oxaliplatin-containing chemotherapy.

The states in the economic model included 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> line therapies and a state for patients who had surgical resection. The rate of surgical resection was a key driver of the result and it was assumed, based on published studies, that patients who had successful resection were tumour-free and had an increase in their mean life expectancy of 4.76 years. Treatment duration with cetuximab was a maximum of 16 weeks.

Clinical data for the model were taken from a range of sources such as the pivotal studies and also other published trials. The rate of surgical resection was assumed in the base case to be 35% for cetuximab compared to 22% for FOLFOX alone or 9% compared to FOLFIRI alone. The rates for FOLFOX and FOLFIRI alone were taken from a published study but the rate for cetuximab appeared to be based on the advice of clinical experts during the recent NICE Single Technology Appraisal of cetuximab.

Resource use and costs were estimated by assumption or published sources. Utility values were estimated from EQ-5D data collected during one of the pivotal studies and in the base case assumed that utility for patients treated with cetuximab is the same as for patients on FOLFOX or FOLFIRI alone. Utility values for other states in the model were taken from published sources or estimated by assumption.

A Patient Access Scheme (PAS) was submitted by the manufacturer and assessed by the Transitional Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Through this scheme, a discount is given on the acquisition cost of cetuximab.

The base case results indicated that cetuximab + FOLFIRI v FOLFIRI resulted in an incremental cost-effectiveness ratio (ICER) of £27,548 (incremental costs of £17,368 and additional QALYs of 0.63). For cetuximab + FOLFOX v FOLFOX the ICER was £36,646 (incremental costs of £16,138 and additional QALYs of 0.44). Taking account of the effects of the PAS, the ICER for cetuximab + FOLFOX v FOLFOX was £26,763 (incremental costs of £11,786 and additional QALYs of 0.44) and for cetuximab + FOLFIRI v FOLFIRI was £22,802 (incremental costs of £14,390 and 0.63 additional QALYs).

A range of one-way sensitivity analyses were presented. For the 'with PAS' ICER, using resection rates of 43% v 22% improved the ICER to £21,056. Using rates of 30% v 22% increased the 'with PAS' ICER to £32,688. Applying a relative risk of death post-resection of 1.5 increased the 'with PAS' ICER to £35,606. Using a lower utility value on cetuximab treatment of 0.73 increased the base case ICER to £28,427. For the FOLFOX (without PAS) sensitivity analysis, using a time horizon of 10 years increased the ICER to £40,655. Again, most upward sensitivity was seen when using higher costs of liver resection and a discount rate of 6% on health gain (ICERs of £39,356 and £40,394 respectively). For the FOLFIRI comparison, applying a relative risk of death post-resection of 1.5 increased the ICER to £35,383.

There were a number of issues with the analysis;

- The results were sensitive to the assumptions made regarding the outcome of successful surgery and while the estimates were noted as being reasonable by SMC experts, there is a general lack of robust data in this area.
- As with many evaluations, the model used information from a range of sources and clinical populations, with relatively short follow-ups, and thus this introduced uncertainty into the outcomes.

Resection rates in the model were a key driver of the outcomes and these were based on the advice given during the NICE STA rather than clinical data.

The SMC modifiers used in appraising new medicines were considered and the Committee was of the view that the use of cetuximab with FOLFIRI or FOLFOX offers the possibility to bridge to another definitive therapy in a defined proportion of patients. Although there were some limitations in the economic analysis, the economic case was demonstrated when the benefits of the PAS were included.

## Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Beating Bowel Cancer
- Bowel Cancer UK

## Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN); Guideline number 67. Management of Colorectal Cancer; a national clinical guideline, published March 2003. A review report in 2007 indicated that from new evidence, new areas could be added to the guideline and recommendations could be updated.

National Institute for Health and Clinical Excellence (NICE); a cancer service guideline: Improving outcomes in colorectal cancer, published in 2004.

National Comprehensive Cancer Network (NCCN) – Clinical practice guidelines in oncology (Colon Cancer and Rectal Cancer), V.3.2009, published August 2009.

European Society for Medical Oncology (ESMO): Advanced colorectal cancer; clinical recommendations for diagnosis, treatment and follow-up, published in 2009.

## Additional information: comparators

The management of metastatic colorectal cancer is mainly palliative and involves a combination of specialist treatments (such as palliative surgery, chemotherapy and radiation), symptom control and psychosocial support. Chemotherapy treatment options include oxaliplatin/fluorouracil/folinic acid and irinotecan/fluorouracil/folinic acid regimens. In Scotland, SMC experts also use combination therapy with oxaliplatin/capecitabine.

## Cost of relevant comparators

Name of regimen	Details of regimen	Cycle length	Cost per cycle (£)	Cost per 26 weeks (£)
<b>cetuximab + FOLFOX-4</b>	<p><b>cetuximab 400mg/m<sup>2</sup> iv infusion for 1<sup>st</sup> dose, then 250mg/m<sup>2</sup> thereafter, D1 and D8</b></p> <p><b>oxaliplatin 85mg/m<sup>2</sup> iv infusion, D1</b></p> <p><b>folinic acid 200mg/m<sup>2</sup> iv infusion, D1 and D2</b></p> <p><b>fluorouracil 400mg/m<sup>2</sup> iv bolus then 600mg/m<sup>2</sup> iv infusion, D1 and D2</b></p>	<b>2 weeks</b>	<p><b>First Cycle: 2,961</b></p> <p><b>Subsequent cycles: 2,484</b></p>	<b>32,763</b>

<b>cetuximab + FOLFIRI</b>	<b>cetuximab 400mg/m<sup>2</sup> iv infusion for 1<sup>st</sup> dose, then 250mg/m<sup>2</sup> thereafter, D1 and D8 irinotecan 180mg/m<sup>2</sup> iv infusion, D1 folinic acid 400mg/m<sup>2</sup> iv infusion, D1 fluorouracil 400mg/m<sup>2</sup> iv bolus then 2400mg/m<sup>2</sup> iv infusion, D1</b>	<b>2 weeks</b>	<b>First Cycle: 2,764 Subsequent Cycles: 2,287</b>	<b>30,208</b>
FOLFOX-4	oxaliplatin 85mg/m <sup>2</sup> iv infusion D1 folinic acid 200mg/m <sup>2</sup> iv infusion D1 and D2 fluorouracil 400mg/m <sup>2</sup> iv bolus then 600mg/m <sup>2</sup> iv infusion D1 and D2	2 weeks	893	11,613
FOLFIRI	irinotecan 180mg/m <sup>2</sup> iv infusion, D1 folinic acid 400mg/m <sup>2</sup> iv infusion, D1 fluorouracil 400mg/m <sup>2</sup> iv bolus then 2400mg/m <sup>2</sup> iv infusion, D1	2 weeks	697	9,058
CapOx (also known as XELOX)	oxaliplatin 130mg/m <sup>2</sup> iv infusion, D1 capecitabine 1000mg/m <sup>2</sup> orally twice daily, D1-14	3 weeks	1041	*6245

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 01 October 2009. D = day, iv = intravenous. Costs are based on a body surface area of 1.8m<sup>2</sup>. Costs per 26 weeks are calculated for complete cycles administered during this period. Calculations assume that unused drug will be discarded and a whole number of vials will be used. Costs calculated for the racemic form of folinic acid where appropriate. \*Experts advise that this treatment is only given for 6 cycles for metastatic disease.

### **Additional information: budget impact**

The manufacturer estimated the gross drug budget impact of using cetuximab would be £274k in year one rising to £1.7m in year five. Accounting for additional drug administration costs the manufacturer estimated an overall budget impact of £1.8m in year five.

Two hundred and eighteen patients were assumed to be eligible in year one rising to 228 in year five. Market share was estimated at 15% in year one rising to 90% in year five, to give a treated patient population of 33 in year one rising to 205 in year five.

These estimates included the effect of the PAS being in place in the case of the FOLFOX regimen. The manufacturer estimated a year five cost of £2.5m including administration costs if the PAS was not in place.

It should also be noted that the figures used the expected mean costs of cetuximab from the economic evaluation and these appeared comparatively low.

**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 **18 December 2009**.*

*Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards together with the SMC advice.*

*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.*

*The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.*

Merck Serono, data on file. Clinical Study Report; CRYSTAL, EMR 62 202-013

Merck Serono, data on file. Clinical Study Report; OPUS, EMR 62 202-047

Merck Serono, data on file. Clinical Study Report; Crystal KRAS Addendum EMR 62202-013 Section 3 KRAS Wild Type Subjects.

Merck Serono, data on file. Clinical Study Report; OPUS KRAS Addendum EMR 62202-047 Section 3 KRAS Wild Type Subjects.

The European Medicines Agency (EMA). European Public Assessment Report. Cetuximab (Erbix<sup>®</sup>). EMA/H/C/000558/II/0020. EMA H-C-558. <http://www.emea.europa.eu>